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MRCP (GLASGO-UK), MRCP-IRELAND



NOTES & NOTES

for MRCP, part 1 & 2

Third edition Notes & Notes

For MRCP

Volume 1

Ву

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Foreword

With the grace of the Almighty Allah, I have introduced the third edition of the popular book, the Notes & Notes for MRCP Part & 2.

The MRCP exam requires a wide range of information, particular thinking, and question directed experience.

This book is directed mainly at those who need comprehensive revision of the topics which commonly appear in the written MRCP exams.

It will be helpful to go through these topics before you start solving the best of the five questions; it is also recommended to go quickly over this book in the last few weeks before the day of your exam.

This new edition contains the new published guidelines.

I hope you will find the maximum benefits from this book to get through MRCP written exams.

To practice the best of five questions we advise you to join the best website for MRCP passonexam.com

For any enquiry or comment, please do not hesitate to contact me.

"The mind is not a vessel to be filled, but a fire to be kindled." – **Plutarch.**

March - 2022
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The 10 Golden Tips for MRCP written exams you will ever need

- 1. For MRCP, do not read hard; read smart.
- 2. Three to six months is usually enough for preparation.
- 3. Practice the best of the five questions as much as possible.
- 4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
- 5. Remember, you are getting ideas and concepts from the questions.
- 6. Time factor in the exam room is the leading killer after poor preparation.
- 7. Manage your time wisely.
- 8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
- Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
- 10. Practice, practice and practice.



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Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Endocrinology & Metabolism

Updated 2022

Pituitary gland conditions

Antidiuretic hormone (ADH) (Vasopressin)

Overview

- Synthesized in the supraoptic nucleus of the hypothalamus.
- Stored and secreted from the posterior pituitary gland
- it contains arginine, so called arginine vasopressin (AVP)
- · Vasoconstrictive effects at higher levels
- Increase of urea reabsorption in the collecting duct: increases the corticomedullary gradient and facilitates urine concentration
- ACTH release

Functions

- Antidiuresis: Act on V2 receptors → ↑↑ transcription and insertion of water (Aquaporin-2) channels into the apical membrane of distal convoluted tubule and collecting duct epithelial cells → ↑↑ water permeability → ↑ water reabsorption (retain water in the body) → excretion of more concentrated urine, i.e., antidiuresis.
- Act on V1 receptors → Increase smooth muscle contraction (Vasoconstriction, uterine, GI and indirectly ↓coronary artery blood flow).
- Increase release of von Willebrand & factor VIII., (Desmopressin used for haemophilia A & Von Willebrand disease).
- 4) Increase platelet aggregation, (prothrombotic at high dose).

Vasopressin receptors

Receptor	Second messenger	Location	Action	Agonist
V 1 or (V1a)	G protein- coupled, phosphatidyli nositol/ calcium	 ◆ vascular smooth muscle, ◆ platelet, ◆hepatocytes, ◆ myometrium 	 ◆vasoconstriction, ◆ myocardial hypertrophy, ◆ platelet aggregation, ◆ glycogenolysis, ◆ uterine contraction 	◆Terlipressin → ↑ splanchnic VC → ↓ esophageal varices bleeding. ◆ Felypressin → prolong the action of local anesthesia (safer than epinephrine in cardiac patients)
V3 or (V1b)	G protein- coupled, phosphatidyli nositol/ calcium	anterior pituitary gland	releases ACTH, prolactin, endorphins	
V2	Adenylate cyclase/	Renal basolateral membrane of collecting duct,	Anti-diuresis (Insertion of aquaporin- 2 channels)	◆ Vasopressin (weak , short acting , given SC or IM) ◆ Desmopressin (more potent, long acting, given intra-nasally)
VZ	cAMP	Extra renal (vascular endothelium)	↑↑ release of von Willebrand & factor VIII.	Desmopressin (used for haemophilia A & Von Willebrand disease)

Factors increase secretion of vasopressin (stimulatory factors):

- Increased osmolality of plasma (The main stimulus).
- Reduced extracellular volume, hypovolaemia, blood loss, and hypotension (less sensitive stimulus).
- decreased thirst perception and reduced fluid intake.
- · Advancing age
- Angiotensin II
- Hypoglycemia
- Increased pain
- Opiates
- Nicotine
- Antineoplastic drugs
- Carbamazepine

Factors decreases secretion of vasopressin (inhibitory factors):

- · genetic conditions (Wolfram syndrome),
- tumours (Craniopharyngioma, Germinoma),
- inflammatory conditions (Sarcoidosis, Histiocytosis).
- Ethanol (alcohol) → ↓↓ calcium-dependent secretion of AVP
- Atrial natriuretic peptide, by inhibiting Angiotensin II-induced stimulation of AVP secretion
- Cortisol

MRCPI-part-1- January 2018: H/O RTA + rapid pulse and low BP + low Na.

- What is the most likely explanation for this patient's hyponatremia?
 - ⇒ Physiologic ADH (vasopressin) secretion
 - Hyponatremia that develops after massive hemorrhage is likely dilutional.
 - When baroreceptors detect decreases in effective arterial volume, such as after massive blood loss, they cause antidiuretic hormone (ADH) to be released from the pituitary gland to increase renal reabsorption of free water, diluting serum sodium levels and causing hyponatremia.
- What is the appropriate management of this patient?
 - ⇒ normal saline.
 - Management of hypovolemic hyponatremia includes volume repletion with normal saline.
 - Correction of hypovolemia removes the stimulus to release ADH, causing free water excretion by the kidneys, which leads to rapid correction of serum sodium levels
 - volume repletion with normal saline must occur at a slow rate, because rapid correction of hyponatremia can cause central pontine myelinolysis.

May 2016 exam -part-1: Which adaptive mechanism that prevent dying from dehydration? → Increase of aquaporin-2 in the collecting duct.

ADH (vasopressin) → ↑ aquaporin-2 expression → ↓ water excretion → protect against dehydration

MRCPUK-part-1-january-2018: You are reviewing a patient with a history of cranial diabetes insipidus. He is passing 4–6 litres of urine per day.

Expression of which channel is likely to be decreased most in the collecting duct?

- → Aquaporin 2
 - It is found in the apical membranes of collecting duct principal cells.
 - Aquaporin 2 gene expression is increased by vasopressin, which leads to increased re-absorption of free water. Expression is therefore downregulated in response to cranial diabetes insipidus.

Syndrome of inappropriate ADH secretion (SIADH) (↑↑ ADH)

Definition

• The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disorder of impaired water excretion caused by the inability to suppress the secretion of antidiuretic hormone (ADH) leading to euvolaemic, hypotonic hyponatraemia.

Causes

Category	Examples
Malignancy	 Small cell lung cancer (The most common cause) Less common head and neck cancer, olfactory neuroblastoma
Neurological	Stroke, subarachnoid haemorrhage, subdural haemorrhage Meningitis/encephalitis/abscess
Infections	Pneumonia, tuberculosis, symptomatic HIV,
Drugs	 Sulfonylureas , Thiazides SSRIs, tricyclics, mono-amine oxidase uptake inhibitors, phenothiazines carbamazepine vincristine , vinblastine cyclophosphamide, chlorpropamide omeprazole
Other causes	 Surgical procedures porphyrias (SIADH is associated with acute intermittent porphyria)

Mechanisms

- ↑↑ (ADH)→ ↑↑ water retention → Euvolemic hyponatraemia (dilutional effects) → low plasma osmolality + high urine osmolality with an elevated urine sodium (above 20 mmol/L)
- Osmotic fluid shifts → Cerebral edema and ↑ intracranial pressure

Features

- Symptoms of hyponatremia (usually asymptomatic until the sodium level falls <u>below 120</u> mmol/l)
 - ➡ Mild: anorexia, nausea, vomiting, headache, muscle cramps (the earliest symptoms of acute hyponatremia are nausea and vomiting.)
 - ⇒ **Moderate:** muscle weakness, lethargy, confusion
 - ⇒ **Severe:** seizures, altered consciousness
- Normotensive
- · Symptoms of the underlying condition

Diagnostic criteria: SIADH can only be diagnosed when the following criteria are satisfied:

- The patient is clinically euvolaemic (no clinical evidence of fluid overload (oedema) or dehydration)
- 2. ↓ Plasma sodium (<134 mmol/l) → hypoosmolality (<280 mOsmol/kg)
- 3. ↑ Urine sodium (>20 mmol/l) and osmolality (>100 mOsmol/kg) → concentrated urine
- 4. Normal thyroid, adrenal, and renal function.
 - ⇒ It is important to note that normal thyroid is referring to primary hypothyroidism. Euthyroid sick syndrome does not preclude the diagnosis of SIADH.

Diagnostic criteria

Diagnostic criteria for SIADH		
	Clinical and/or laboratory findings	
Hyponatremia	↓ Serum sodium < 135 mEq/L	
Hypoosmolality	↓ Serum osmolality < 275 mOsm/kg	
Concentrated urine	↑ Urine osmolality > 100 mOsm/kg	
Elevated urinary sodium	↑ Urine sodium concentration > 20 mEq/L	
Euvolemia	 No signs of hypovolemia No signs of hypervolemia (e.g. oedema) 	
No alternative causes	 Normal thyroid, adrenal, and renal function → Other causes of euvolemic hypotonic hyponatremia have been excluded (e.g., hypothyroidism, hypercortisolism, AKI) It is important to note that normal thyroid is referring to primary hypothyroidism. Euthyroid sick syndrome does not preclude the diagnosis of SIADH. 	

Differential diagnosis

- Cerebral salt wasting (CSW)
 - ⇒ hypovolaemia, hyponatraemia and grossly elevated urine sodium (>100) in patient with head injury.
 - ⇒ it treated with replacing fluid and sodium losses, whereas SIADH treated with fluid restriction

SIADH patients are usually euvolemic, normotensive, and have no edema. A hyponatremic patient with edema should raise suspicion of other conditions (e.g. congestive heart failure)

Management

Restriction of water intake is the <u>initial treatment of choice</u> for hyponatraemic patients with <u>SIADH who are not at imminent risk of seizures or coma</u>. This precipitates a gradual rise in serum sodium, not greater than the recommended maximum of 8–10 mmol/day.

- Sever acute symptomatic hyponatraemia: (who present with neurologic abnormalities, e.g. seizures or \(\) conscious level).
 - ⇒ hypertonic (3%) saline given via continuous infusion
 - Infusion of hypertonic (3%) saline is reserved for patients with acute severe life-threatening hyponatraemia, usually where sodium is less than 120 mmol/l and there are significant neurological features (i.e. seizures or GCS less than 11).
 - ⇒ correction must be done slowly to avoid precipitating central pontine myelinolysis
 - The sodium serum levels may increase by a maximum of 10 mmol/L within 24 hours or 0.5 mmol/L per hour.
- Mild acute OR chronic hyponatraemia: (Na+ ≥ 120 and NO neurological signs)
 - ⇒ 1st line → fluid restriction (the initial treatment of choice)
- Restriction of fluid to a daily intake of less than 800 mL/day.
- patients with subarachnoid hemorrhage are an exception since fluid restriction may promote cerebral vasospasm.
 - ⇒ 2nd line → demeclocycline
- it is a semi-synthetic tetracycline antibiotic →reduces the responsiveness of the collecting tubule cells to ADH (by inducing nephrogenic diabetes insipidus)
 - ⇒ 3rd line → ADH (vasopressin) receptor antagonists have been developed (ie. tolvaptan)
- Side effects → hepatotoxicity, excessive thirst

SIADH initial treatment:

- If there is obvious precipitant (eg: drug) → stop the precipitant agent
- where there is no obvious precipitant → fluid restriction → demeclocycline

Diabetes insipidus (DI)

Diabetes insipidus is characterised by a high plasma osmolality and a low urine osmolality

Definition

 The passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg) due to deficiency of or insensitivity to antidiuretic hormone (ADH).

Types and mechanisms of DI

- Cranial DI: caused by a deficiency of antidiuretic hormone (ADH) (the most common type)
- 2. Nephrogenic DI: caused by insensitivity to ADH (rare)
- Primary polydipsia (dipsogenic DI): caused by a primary defect in osmoregulation of thirst.
- 4. **Gestational DI:** caused by degradation of vasopressin by a placental vasopressinase.

Causes of cranial DI

- Primary
 - ⇒ Idiopathic (the most common primary cause)
 - ⇒ Hereditary (rare): Wolfram's syndrome (DIDMOAD): association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness.
- Secondary
 - ⇒ Brain tumors (especially craniopharyngioma) and cerebral metastasis
 - ⇒ Neurosurgery: usually after the removal of large adenomas
 - ⇒ Traumatic brain injury, pituitary bleeding, subarachnoid hemorrhage
 - ⇒ Pituitary ischemia (e.g., Sheehan syndrome, ischemic stroke)
 - ⇒ Infection (e.g., meningitis)
 - ⇒ Sarcoidosis

Wolfram's syndrome or the DIDMOAD syndrome is characterised by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness

Causes of nephrogenic DI

- · Genetic: two forms:
 - 1. vasopressin-2 receptor (V2 ADH) mutation
 - the more common form, X linked (usually male are affected)
 - 2. mutations in the aquaporin-2 gene $\rightarrow \downarrow$ water reabsorption in the distal tubule.
 - less common form , autosomal recessive
- · Electrolytes:
 - ⇒ hypercalcaemia
 - \Rightarrow hypokalaemia \rightarrow desensitization of renal tubules to (ADH) \rightarrow \uparrow water excretion
- Drugs: the commonest precipitants
 - ⇒ tetracycline (demeclocycline)
 - ⇒ **lithium** → enters the principal cells of the collecting duct through the epithelial sodium channels (ENac) → **inhibits signalling pathways that involve glycogen synthase kinase type 3 beta (GSK3beta)** → dysfunction of aquaporin-2 water channel → nephrogenic DI.
- Tubulo-interstitial disease: obstruction, sickle cell trait, pyelonephritis, Sjögren's syndrome.
- Pregnancy (combined renal hyposensitivity to ADH, increased placental elimination of ADH, lowered thirst threshold and effect of fluid retention)

Hypokalaemia is a rare cause of polyuria and polydipsia

Nephrogenic DI is the most common adverse effect of lithium and occurs in up to 40% of patients

Features

- Polvuria
 - ⇒ urine output is > 50 ml/kg per day (3000 ml for a 60-kg female).
 - Nocturia → Restless sleep, daytime sleepiness (In the absence of nocturia, diabetes insipidus is very unlikely)
- Polydipsia

Diagnosis

In suspected DI the most appropriate next investigation is → Urine and plasma osmolality (non-invasive first step)

- High plasma osmolality
 - ⇒ plasma osmolality >305 mOsmol/kg
 - ⇒ serum [Na] >145 mmol/L
- Low urine osmolality
 - ⇒ urine osmolality <200 mOsm/kg
 </p>
 - ⇒ urinary [Na] 20-60 mmol/L
 - ⇒ urinary specific gravity <1.005.
- Water deprivation test with response to desmopressin (The patient is deprived of fluids for up to eight hours or 5% loss of body weight, following which desmopressin (DDAVP®) 2 micrograms (IM) is given).
 - ⇒ CDI → ↓ urine osmolality and ↑ serum osmolality **CORRECTED** by Desmopressin administration (plasma osmolality normalizes and urine osmolality rises).
 - ⇒ NDI → low urine osmolality and elevated serum osmolality, with no significant response to desmopressin.
- CT scan or MRI of the head: If CDI is diagnosed, to rule out brain tumors

Management

- Central DI
 - ⇒ Mild CDI (urine output 3-4 litres/24 hours) → increase oral water intake.
 - oral or nasogastric water is the replacement fluid of choice as this route provides a good buffer against rapid changes in serum sodium.
 - \Rightarrow If the urine output continues to be greater than 250 ml/hr \rightarrow **Desmopressin** (Synthetic ADH) is the drug of choice.
- Nephrogenic DI → correct the underlying cause (e.g. stop the responsible drug)
 - ⇒ Thiazide diuretic (eg, hydrochlorothiazide), amiloride (K- sparing diuretic) → act on Distal Convoluted Tubule and inhibit the NaCl cotransporter and thus exaggerate the hypovolemia and increase an already activated renin–angiotensin–aldosterone system (RAAS) further. This mechanism stimulates proximal tubule sodium and water reabsorption resulting in less volume delivery to the collecting tubules where ADH work.
 - ⇒ NSAIDs (indomethacin) → inhibit prostaglandin synthesis, which has antagonistic effects on ADH.
 - ⇒ Amiloride is the drug of choice for lithium induced nephrogenic DI → blocks the epithelial sodium channel (ENac) in the collecting duct where lithium enter and causes DI.

Rate of hypernatraemia correction

- Symptomatic patients with acute hypernatraemia (developed within 48h) → 5mmol/L in the first hour (or until symptoms improve) and is limited to 10mmol/L per 24h.
- No or mild symptoms

 the rate of correction should not exceeding 0.5mmol/L/h and is limited to 10mmol/L/24h.

Fluid status in DI

• Total body water: decrease

Extracellular fluid: increase

• Intracellular fluid: decrease

DI \rightarrow losing hypotonic fluid in the urine $\rightarrow \uparrow$ osmolarity of the extracellular fluid \rightarrow water will flow out of the intracellular compartment and into the extracellular compartment $\rightarrow \uparrow$ extracellular fluid volume and \downarrow intracellular fluid volume.

Which part of the nephron is most affected in diabetes insipidus? Cortical and medullary collecting tubules

If there is hypovolaemic hypernatraemia ((hypotension, tachycardia, poor skin turgor)): The first step is to restore volume with isotonic fluids (0.9% saline).

Water deprivation test

Overview

- The diagnostic test to confirm DI is a water deprivation test.
- The goal of water restriction is to raise the plasma sodium to at least 145 mEq/L and plasma osmolality to 295 mOsmol/kg to stimulate enough ADH release to concentrate urine in normal subjects. If water restriction does not raise the Na and osmolality to this level, hypertonic saline infusion may be necessary.
- Normal plasma osmolality is 285-305 mosmol/kg.
- The normal 24-hour urine osmolality is, on average, **500-800 mOsm**/kg of water.

Method

- Prevent patient drinking water (for a period of 8 h or until 5% of body weight is lost).
- Ask patient to empty bladder
- Patients should be weighed hourly.
- · Test urine volume and osmolality every hour
- Test sodium and plasma osmolality every two hours
- Water deprivation continues until one of the following occurs:
 - Urine osmolality rises and reaches a normal value (> 600 mOsmol/kg) → DI ruled out and primary polydipsia confirmed
 - Where urine osmolality reaches levels above 600 mOsmol/kg without desmopressin, then the diagnosis is primary polydipsia.
 - 2. No change in urine osmolality despite a rising plasma osmolality (> 290 mOsmol/kg)
 - 3. Plasma osmolality > 295-300 mOsmol/kg or sodium ≥ 145 meg/L
- In the latter two situations → administer desmopressin (a synthetic ADH analog) 2 μg intramuscular
 - ⇒ Monitor urine osmolality testing every 30 minutes for 2 hours
 - In CDI: Urine osmolality rises (> 600) after desmopressin administration (renal ADH receptors are intact).
 - In NDI: Urine osmolality remains low after desmopressin administration (defective renal ADH receptors).

Classification of causes of diabetes insipidus on basis of water deprivation and DDAVP® response

	Primary polydipsia (psychogenic polydipsia)	CDI	NDI
Lab findings on presentation	 Hyponatremia (< 137 meq/L) Plasma osmolality: low- normal (255–280 mOsmol/kg) Very low urine osmolality (< 250 mOsmol/kg) 	Mild hypernatremia High-normal plasma mOsmol/kg) or slightl Low urine osmolality ⇒ Partial DI: 300 ⇒ Complete DI:	osmolality(280–290 y elevated –500 mOsmol/kg
Water deprivation test results	Plasma osmolality: normal (275–290 mOsmol/kg) Urine osmolality: rises, reaches normal value (> 600 mOsmol/kg) This result shows that both ADH release and effect are intact.	 Plasma osmolality: ris mOsmol/kg) Urine osmolality: no 	,
Desmopressin administration results	Water deprivation test results confirm diagnosis; no need to administer desmopressin	Plasma osmolality: normalizes (275– 290 mOsmol/kg) Urine osmolality rises	Plasma osmolality remains elevated Urine osmolality remains low

Classification of causes of diabetes insipidus on basis of water deprivation and DDAVP® response					
Urine osmolality after fluid deprivation (mOsm/kg)	Urine osmolality after DDAVP® (mOsm/kg)	Likely diagnosis			
<300	>800	Cranial DI			
<300	<300	Nephrogenic DI			
>800	>800	Primary/psychogenic polydipsia			
<300	>800	Partial cranial DI or nephrogenic DI or PP or diuretic abuse			

A dramatic improvement in the ability of the kidneys to concentrate urine following the administration of DDAVP points towards a diagnosis of cranial diabetes insipidus

Differentiate psychogenic polydipsia from CDI and NDI:

- Patients with this disorder ingest and excrete up to 6L of fluid/day and are often emotionally disturbed.
- Unlike patients with CDI and NDI, they do not have nocturia, nor does increased thirst wake them at night.
- Patients with acute psychogenic polydipsia can concentrate their urine during a water deprivation test but chronic water intake diminishes medullary tonicity in the kidney.
- Patients with long-standing polydipsia are not able to concentrate their urine to maximal levels during water deprivation, a response similar to that of patients with partial central diabetes insipidus.

 However, unlike central diabetes insipidus, patients of psychogenic polydipsia show no response to exogenous ADH after water deprivation. This response resembles nephrogenic diabetes insipidus, but <u>ADH levels</u> are low in psychogenic polydipsia and high in nephrogenic polydipsia.

Polyuria

Definition

defined as a urine output exceeding 3 L/day

Causes

Common (>1 in 10)	Infrequent (1 in 100)	Rare (1 in 1000)	Very rare (<1 in 10 000)
diuretics, caffeine & alcohol diabetes mellitus lithium heart failure	hypercalcaemiahyperthyroidism	chronic renal failureprimary polydipsiahypokalaemia	diabetes insipidus

Thiazide diuretic abuse

 polyuria and polydipsia of recent onset + high calcium, glucose and hypokalaemia, with an elevated bicarbonate. ↑Serum Osmolality > 300

Hyponatraemia (serum sodium less than 135 mEq/L).

Prevalence

• Occurs in up to 30% of hospitalised patients

Classifications

- · based on severity:
 - ⇒ Mild hyponatraemia : serum sodium between 130 and 135 mmol/l
 - ⇒ Moderate hyponatraemia: serum sodium between 125 and 129 mmol/l
 - ⇒ Profound hyponatraemia: serum sodium <125 mmol/l
- based on time of development:
 - ⇒ **Acute** hyponatraemia: hyponatraemia that is documented to exist < 48h.
 - ⇒ Chronic hyponatraemia: hyponatraemia that is documented to exist ≥ 48h.
 - If hyponatraemia cannot be classified, we consider it being chronic

Mechanisms of causes

- 1. water excess
- 2. sodium depletion
- 3. Pseudohyponatraemia: (isotonic hyponatraemia)
 - ⇒ Causes
 - Hyperglycaemia
 - hyperlipidaemia (increase in serum volume)
 - hyperproteinemia (e.g. myeloma)
 - taking blood from a drip arm.
 - ⇒ exclude hyperglycaemic hyponatraemia by measuring the corrected serum Na⁺

- adding 2.4mmol/l to the measured serum sodium for every 5.5mmol/l incremental rise in serum glucose concentration above a standard serum glucose concentration of 5.5mmol/l.
- corrected Na⁺ = measured Na⁺ + 2.4 x (serum glucose mmol 5.5/5.5mmol)
- ⇒ Non-hypotonic hyponatraemia does not cause brain oedema and is managed differently from hypotonic hyponatraemia.

Pseudohyponatraemia is characterised by a normal measured serum osmolarity, however the calculated osmolarity (based on an erroneously low plasma sodium result) is reduced. This results in a raised osmolar gap

Causes of hyponatraemia

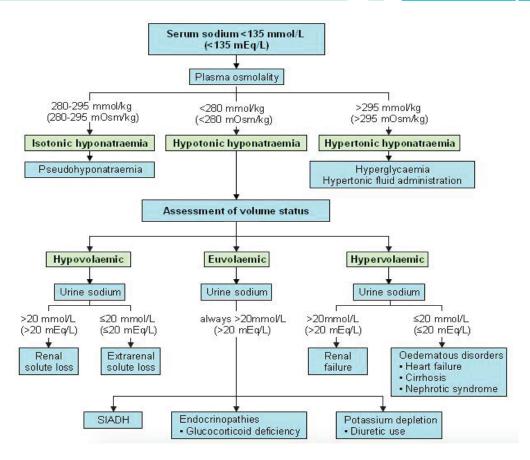
Urinary sodium > 20 mmol/l		Urinary sodium < 20 mmol/l	
Sodium depletion, renal loss (patient often hypovolaemic)	Patient often euvolaemic	Sodium depletion, extra-renal loss (hypovolaemic)	Water excess (patient often hypervolaemic and oedematous)
diuretics diuretic stage of renal failure Addison's	SIADH (urine osmolality > 500 mmol/kg) hypothyroidism	diarrhoea, vomiting, sweating burns, adenoma of rectum	 secondary hyperaldosteronism: heart failure, cirrhosis reduced GFR: renal failure IV dextrose, psychogenic polydipsia

Features

- Fatique, Muscle weakness
- · Gait disturbance. Falls
- Cerebral oedema → Disorientation, Seizures

Investigations

- Urinary sodium and osmolarity levels aid making a diagnosis.
 - ⇒ urinary sodium
 - Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal.
 - may be misleading in the presence of renal impairment or diuretic therapy.



Management

- ascertain volume status as this will determine management.
 - ⇒ Hypovolaemic hyponatraemia
 - Diagnosis may supported by an <u>elevated urea</u> suggesting dehydration.
 - rehydration with sodium chloride 0.9% or a balanced crystalloid (Hartmann's)
 - avoid rapid Na correction to reduce the risk of central pontine myelinolysis.
 - ❖ The rate of Na correction should not exceed 8 mEq/L per day.

⇒ Euvolaemic hyponatraemia

- check urine and serum osmolality. Does the patient meet the criteria for SIADH?
- treat the underlying cause where possible in SIADH
- fluid restriction (500-750mls/day)
- monitor fluid balance and perform daily weights
- consider <u>demeclocycline</u> or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone.

⇒ Hypervolaemic hyponatraemia

- fluid and salt restriction
- consider diuretics
- treat the underlying cause (e.g. cardiac failure)

Hyponatraemia: correction

Acute hyponatraemia is that which occurs within a duration of 48 hours.

Acute hyponatraemia

- predisposing factors to acute hyponatraemia:
 - ⇒ Over consumption of fluids,

 - ⇒ prolonged race duration and inadequate training
- Pathophysiology
 - When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result, patients may die from brain herniation.
- Features
 - ⇒ hyponatraemic encephalopathy which is life threatening and presented with a fit.
- Treatment of Hyponatraemia with severe symptoms
 - ⇒ Hypertonic saline (3%) boluses are the most appropriate treatment to improve neurological status in such patients.
 - 150mls of 3% hypertonic saline over 20 mins
 - check the serum sodium after 20min while repeating an infusion of 150ml 3% hypertonic saline for the next 20min.
 - repeat therapeutic twice or until a target of 5 mmol/l increase in serum sodium is achieved
 - The target sodium by which one should elevate the sodium is 5 mmol/l over the first hour.
 - limit the increase in serum sodium to a total of 10 mmol/l during the first 24h and an additional 8 mmol/l during every 24h thereafter until the serum sodium concentration reaches 130 mmol/l
 - ⇒ Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment.

Hypopituitarism

Definition

- Deficiency of one or more anterior pituitary hormones.
 - ⇒ GH deficiency → growth retardation (during childhood), ↓ bone density, muscle atrophy, hypercholesterolemia
 - ⇒ Prolactin deficiency → lactation failure following delivery
 - ⇒ FSH/LH deficiency → hypogonadotropic hypogonadism (secondary hypogonadism)
 - ⇒ TSH deficiency → secondary hypothyroidism
 - ⇒ ACTH deficiency → secondary adrenal insufficiency
- Hypopituitarism becomes symptomatic when more than 80% of pituitary cells are damaged.

Causes

- Intrasellar/parasellar masses
 - Nonsecretory pituitary macroadenomas (≥ 10 mm in diameter) are the most common cause of hypopituitarism among adults (~ 40% of cases).
 - ⇒ Less common: internal carotid artery aneurysms, meningiomas, craniopharyngiomas,
- Pituitary apoplexy
 - ⇒ results in acute hypocortisolism and hypothyroidism, can present with sudden hypotension and hypovolemic shock
- Sheehan syndrome: postpartum necrosis of the pituitary gland. Usually occurs following
 postpartum hemorrhage but can also occur even without clinical evidence of hemorrhage.
- Traumatic brain injury (especially around the skull base)
- Infiltration of the pituitary and/or hypothalamus
 - ⇒ Hemochromatosis, Sarcoidosis
 - ⇒ Infections: meningitis, TB
- · Empty sella syndrome
- latrogenic
 - ⇒ Hypophysectomy
 - ⇒ Pituitary irradiation
- Congenital
 - ⇒ deficiency of hypothalamic hormones: GnRH deficiency (Kallman syndrome)

Features (depends on which hormone is deficient).

- Growth hormone deficiency: The first hormone to fall is the growth hormone
 - ⇒ in children →short stature
 - ⇒ in adults → tiredness, weight gain
- ACTH deficiency → weight loss, weakness, Postural hypotension, chronic hyponatremia, hypoglycemia
- TSH deficiency → weight gain, cold intolerance, lethargy, constipation, dry skin
- FSH/LH deficiency
 - ⇒ Women → primary amenorrhea (delayed puberty), secondary amenorrhea, irregular menstrual cycles. infertility
 - ⇒ The presence of regular menstrual cycles in women rules out hypogonadism.
 - ⇒ Men → delayed puberty, loss of libido, infertility, testicular atrophy.
- Intrasellar/parasellar masses (e.g., pituitary macroadenomas, craniopharyngiomas) can manifest with headache, visual field defects (bitemporal hemianopsia), and/or diplopia
- Pituitary apoplexy → Severe headache, bilateral hemianopia, diplopia (due to damage to CN III), sudden hypotension.
- PRL deficiency is rare, except in Sheehan's syndrome → failure of lactation
- **Houssay phenomenon:** Amelioration of diabetes mellitus in patients with hypopituitarism due to reduction in counter-regulatory hormones.

In the majority of cases, the development of hypopituitarism follows a characteristic order, with secretion of **GH**, then **gonadotrophins** being **affected first**, **followed by TSH** and **ACTH** secretion at a later stage.

Investigations

- · Insulin stress test
 - the gold standard dynamic test for the diagnosis of ACTH and GH deficiency in patients with suspected hypopituitarism.
 - ⇒ a weight-based dose of intravenous insulin to achieve a hypoglycaemia level below 2.2 mol/l. With normal pituitary function GH and cortisol should rise
 - ⇒ Contraindications: epilepsy, ischaemic heart disease and adrenal insufficiency
- central/secondary adrenal insufficiency: low morning cortisol level + Low to normal ACTH
- thyroid function tests → secondary hypothyroidism:↓ or normal TSH with ↓ serum free T4 and ↓ serum free T3
- MRI brain

Management

- Hydrocortisone: the most important replacement therapy to be started first to avoid the possibility of precipitating an adrenal crisis.
 - ⇒ Fludrocortisone is only necessary in patients with adrenal insufficiency who are unable to maintain normal blood pressure control.
- Thyroxine replacement: should be begun after commencing hydrocortisone because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis.
- **GH therapy:** licensed for treatment of symptoms with reduced quality of life on adult growth hormone deficiency assessment (AGHDA) questionnaire score.
- Testosterone: the most appropriate treatment to prevent the progression of bone loss
- In addition to pituitary hormone replacement, the underlying cause of hypopituitarism should be treated.

Patients with TSH deficiency should not be treated with levothyroxine until ACTH deficiency has been ruled out and/or treated because levothyroxine increases the clearance of cortisol and may precipitate an adrenal crisis

Growth hormone (GH)

Secretion

- Hypothalamus → release Growth hormone releasing hormone (GHRH) → stimulates the somatotrophs in the anterior pituitary gland → release GH.
- Secreted in a pulsatile manner. The highest level of GH is seen around midnight during the sleep period.
- GHRH uses two second messengers <u>cAMP and IP3/Ca2+</u> to stimulate growth hormone release.

Which signaling pathways does growth hormone (GH) use?
⇒ Tyrosine kinase receptor

Mechanism of action

- Direct action via tyrosine kinase receptor on target tissues, such as skeletal muscle, liver, or adipose tissue
 - \Rightarrow \downarrow Glucose uptake into cells (\uparrow insulin resistance) \rightarrow \uparrow Blood insulin levels
 - ↑ Lipolysis
 - ⇒ ↑ Protein synthesis in muscle
 - ⇒ ↑ Amino acid uptake
- Indirect action via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver
 - ⇒ Growth stimulation
 - ⇒ Anabolic effect on body

Growth hormone (GH) counteracts in general the effects of insulin on glucose and lipid metabolism but shares protein anabolic properties with insulin.

GH along with cortisol and adrenalin (called counter-regulatory hormones) tell the body to increase the availability of glucose – so it counters the effect of insulin.

GH regulation

↑ GH secretion	↓ GH secretion	
Deep sleep	Somatostatin	
 Fasting → Hypoglycaemia 	 Beta adrenergic activity 	
 Alpha adrenergic activity 	 Hyperglycaemia (initially) 	
Stress	 Obesity 	
Exercise	 Free fatty acids 	
 Ghrelin the "hunger hormone" 	 Hypothyroidism 	
 Amino acids (Arginine) 	• IGF-1	
 Sex steroids (estrogen or testosterone) 	 Pregnancy 	
Puberty	 Increased age 	
• CKD	Glucose	
 Thyroid hormone, thyroxine 	Chronic glucocorticoid	
Estrogen, testosterone	therapy	
Short-term glucocorticoid exposure		

- An increase in GH levels is seen in patients with Type 1 DM, while in patients with Type 2 DM the levels may be increased, normal or decreased.
- GH levels increase in malnutrition in contrast to a decrease in IGF-1 levels.
- In poorly controlled diabetics GH levels are invariably raised whilst normal or low levels of IGF-I are found, indicating a dissociation between the two factors.

Conditions associated with GH disorders

- · GH deficiency: resulting in short stature
- · excess GH: acromegaly

Growth hormone deficiency (GHD)

Causes

- Pituitary tumours or their treatment, (e.g. surgery, cranial irradiation) is the most common cause.
- Any other cause of hypopituitarism (see hypopituitarism topic)

Features

- In infancy are hypoglycemia and micropenis is the primary manifestations
- In <u>early childhood</u>: growth failure is the primary manifestation. causes premature fusion of the epiphyseal portion of the bone.
- In adults
 - ↑↑ fat mass
 - ⇒ ↓↓ lean body mass
 - ⇒ ↓↓ bone mineral density (BMD) → osteopenia/osteoporosis
 - ⇒ ↓ energy, ↓ quality of life (QoL)
 - ⇒ ⊥⊥ sweating → Dry skin
 - ⇒ ↑↑ greater mortality , ↑↑ cardiovascular risk
 - ⇒ ↑↑ insulin resistance
 - ⇒ Dyslipidaemia (↑LDL).

Diagnosis

- Decreased serum insulin-like growth factor-1 (IGF-1) levels: may be normal in up to 50%.
- Dynamic tests of GH secretion
 - ⇒ Insulin tolerance test (ITT): the gold standard for the diagnosis
 - insulin-induced hypoglycaemia → GH response of less than 9 mU/L (3 ng/ml) → GHD
 - Causes of <u>false positive</u> test: Obesity →↓ GH response to insulin → false positive test
 - Contra-indications to ITT:
 - seizures (eg: in epilepsy)
 - IHD, Abnormal ECG
 - basal cortisol levels <100 nmol/L</p>
 - Glycogen storage disease
 - Elderly (due to high risk of hypoglycaemia)
 - ⇒ Alternative test if ITT is contraindicated:
 - arginine-GHRH stimulation test
 - glucagon-GH-releasing hormone stimulation test
- Two tests of GH stimulation test are required before making the diagnosis.

Treatment → Subcutaneous injections of recombinant human growth hormone.

- Criteria for GH treatment: only if all the following three criteria are met
 - 1- Severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/ml) during an insulin tolerance test.
 - 2- Impairment of Quality of Life (QoL): 'Quality of life assessment of growth hormone deficiency in adults' (QoL-AGHDA) score ≥ 11.
 - 3- Treatment for other pituitary hormone deficiencies

Adverse effects of GH replacement

- Sodium and water retention
 - ⇒ Weight gain
 - ⇒ Carpal tunnel syndrome
- Hyperinsulinaemia
- Arthralgia (possibly due to intra-articular cartilage swelling)
- Myalgia
- Benign intracranial hypertension (resolves on stopping treatment)

Contraindications to GH replacement

- Active malignancy
- Benign intracranial hypertension
- Pre-proliferative/proliferative retinopathy in diabetes mellitus

Which treatment is most appropriate for patients with preserved pituitary function and deficiencies in growth hormone (GH) and adrenocorticotrophic hormone (ACTH)?

- Cortisol replacement therapy only.
 - ⇒ GH deficiency can be caused by hypoadrenalism. Concomitant cortisol and GH replacement therapies are not appropriate because cortisol alone may be sufficient to restore GH secretion.

MRCP-UK. SCE .Sample question

patients with childhood-onset GHD who are candidates for GH therapy after adult height achievement. What is the most appropriate next step in management?

→ should be retested for GHD

Acromegaly

Approximately 30% of growth hormone (GH) secreting pituitary tumours is associated with mutation of the Gs protein alpha subunit

Definition

 Acromegaly is the clinical condition resulting from prolonged excessive GH and hence IGF-1.

Epidemiology

Most cases are diagnosed at 40–60 years.

Causes

- Pituitary adenoma (95%)
- ectopic GHRH or GH production by tumours e.g. pancreatic
 - ⇒ mechanism: GH secreting tumours → mutation in the alpha sub-unit of the stimulatory guanosine triphosphate (GTP) binding protein → persistent elevation of cyclic adenosine monophosphate (cAMP) → production of excess growth hormone.

Features

- Headaches
- Visual field loss (attributable to optic chiasmal compression), diplopia (due to cranial nerve palsy)
- · Increase in shoe size
- Increased sweating: due to sweat gland hypertrophy
- Hands: spade-like hands
- Face: general coarse facial appearance, prognathism, , eyes, bitemporal hemianopia
- Mouth: large tongue → <u>Sleep apnea</u>, interdental spaces

Macroglossia: Causes

- Hypothyroidism
- Acromegaly
- Amyloidosis
- Duchenne muscular dystrophy
- Mucopolysaccharidosis (e.g. Hurler syndrome)
- Down's syndrome

Complications

- Hypertension (40%).
- Insulin resistance and impaired glucose tolerance (40%)/diabetes mellitus (20%).
- Obstructive sleep apnoea: due to soft tissue swelling in nasopharyngeal region.
- ↑ risk of colonic polyps and colonic carcinoma
- ↑ Ischaemic heart disease and cerebrovascular disease.
- ↑ Congestive cardiac failure and possible ↑ prevalence of regurgitant valvular heart disease.
- Cardiomyopathy → heart failure
- · Osteoarthritis, Arthralgia, Pseudogout
- Carpal tunnel syndrome: Positive Tinel's sign
- 6% of patients have MEN-1, hypercalcemia → primary hyperparathyroidism → MEN 1.

Investigations

The diagnostic test for acromegaly is an oral glucose tolerance with growth hormone measurements

- Serum insulin-like growth factor 1 (IGF-1)
 - ⇒ IGF-1 measurement is the most appropriate initial investigation
 - ⇒ May also be used as a screening test , sometimes used to monitor disease
 - ⇒ Normal IGF-1 levels rule out acromegaly
 - \Rightarrow If \uparrow IGF-1 \rightarrow conduct OGTT with baseline GH \rightarrow measure GH after 2 hours:
 - lacktriangledown if GH suppressed ightarrow acromegaly ruled out
 - if GH not suppressed: confirmed acromegaly → conduct pituitary MRI
 - ⇒ Growth hormone (GH) levels vary during the day and are therefore not diagnostic.
- Oral glucose tolerance test (OGTT) with serial GH measurements.
 - **⇒** The definitive test
 - \Rightarrow Lack of suppression of GH to < 1 $\mu g/L$ following documented hyperglycemia during an oral glucose load.
 - ⇒ False +ves: Chronic renal and liver failure, malnutrition, diabetes mellitus, heroin addiction, adolescence (due to high pubertal GH surges).

- Assess for other pituitary functions
- **Pituitary MRI**: usually demonstrates the tumour (98%)
- If no pituitary tumor detected → serum GHRH + radiology of the chest and abdomen to detect ectopic GHRH-secreting tumor (usually a GHRH-secreting carcinoid of lung or pancreas.)
- Associated laboratory features
 - ⇒ Serum calcium: GH stimulates renal 1α-hydroxylase→↑ 1,25-Dihydroxycholecalciferol (DHCC) → hypercalcaemia → hypercalciuria (which occurs in 80%) →↑likelihood of renal stones.
 - ⇒ elevated Phosphate levels
 - ⇒ Raised prolactin in 1/3 of cases → galactorrhoea

In active acromegaly with associated diabetes mellitus → There is insulin resistance

Acromegaly \rightarrow ↑risk of colon cancer \rightarrow regular colonoscopy screening, starting at the age of 40 years.

Management

Trans-sphenoidal surgery is first-line treatment for acromegaly in the majority of patients

Octreotide can be used as an adjunct to surgery in patients with acromegaly

- Surgery: transsphenoidal adenomectomy
 - ⇒ first-line treatment for acromegaly in the majority of patients
 - ⇒ the percentage likelihood of cure from surgery: > 85% for microadenomas and 40–50% for macroadenomas
- Medication: In patients with inoperable tumors or unsuccessful surgery, medication
 and radiotherapy are indicated to reduce tumor size and limit the effects of GH and IGF-1.
 - ⇒ Somatostatin analogs (e.g., octreotide, lanreotide, pasireotide)
 - first line medical therapy.
 - side effects: gallstone disease
 - ⇒ **Dopamine agonists** (e.g., **bromocriptine**, cabergoline):
 - less effective than somatostatin analogues.
 - may be helpful if there is coexistent secretion of PRL → significant tumour shrinkage.
 - Cabergoline is more effective than bromocriptine
 - ⇒ GH receptor antagonists (e.g., pegvisomant)
 - Indicated for somatostatin non-responders. Third-line treatment when surgery, radiotherapy and somatostatin analogues are not effective.
 - Very effective decreases IGF-1 levels in 90% of patients to normal
 - Pre-operative: may improve metabolic risk factors for surgery, such as hypertension and hyperglycaemia
 - Monitoring: liver function tests → discontinue pegvisomant if the transaminases are greater than 3-fold elevated.

Radiotherapy

- ⇒ Indications: residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated.
- ⇒ stereotactic radiotherapy (SRT) is preferred over conventional radiation therapy
- ⇒ Side effects: Danger of hypopituitarism → do annual hormonal testing

Long acting somatostatin analogue

- Mode of action → ↓↓ meal-time related superior mesenteric artery blood flow
- One intra-muscular injection should be given every 14 days.
- **Common side effects:** pain at injection site, GIT disturbances, Cholelithiasis, Sinus bradycardia, Hypoglycaemia, hyperglycaemia

Which test is the best way to monitor for recurrence after trans-sphenoidal surgery for resection of a growth hormone-secreting pituitary adenoma?

Insulin-like growth factor 1(IGF-1)

Prognosis

 Left ventricular failure is the most common cause of death if treatment is unsuccessful

Laron's syndrome

Definition

 an <u>autosomal recessive</u> disorder characterized by an <u>insensitivity to (GH)</u>, usually caused by a mutant growth hormone <u>receptor</u>.

Features

- · short stature
- Reduced risk of developing acne, cancer and diabetes mellitus type II.
- Seizures are frequently seen secondary to hypoglycemia.
- low levels of insulin-like growth factor (IGF-1) and its principal carrier protein, insulin-like growth factor binding protein 3.

Treatment

- injections of recombinant IGF-1.
- Not respond to growth hormone treatment due to a lack of GH receptors.

Nelson syndrome (post adrenalectomy syndrome)

Aetiology

- bilateral adrenalectomy in patients with a previously undiscovered pituitary adenoma
- occurs in 30% of patients adrenalectomised for Cushing's disease.

Pathophysiology 1 4 1

 Bilateral adrenalectomy → no endogenous cortisol production → no negative feedback from cortisol on hypothalamus → increased CRH production → uncontrolled enlargement of preexisting ACTH-secreting pituitary adenoma → increased secretion of ACTH and melanocyte-stimulating hormones (MSH) → symptoms of pituitary adenoma and ↑ MSH.

Features

- Headaches, bitemporal hemianopia (mass effect)
- Cutaneous hyperpigmentation: arises from the MSH products of the proteolysis of POMC, which also produces ACTH.

Diagnosis

- High levels of beta-MSH and ACTH
- Pituitary adenoma on MRI confirms the diagnosis.

Treatment

 Surgery (e.g., transsphenoidal resection) and/or pituitary radiation therapy (e.g., in the case of tumor residues after surgery)

Monitorina

- ACTH levels
- serial pituitary imaging.

Pituitary adenoma

Epidemiology

- Small pituitary tumours (<4 mm) are common and have been reported in up to 10% of MRIs in the general population.
- · Only a small fraction of such tumours are associated with clinical features suggestive of pituitary disorder.

Classifications

- According to size:
 - ⇒ Microadenoma: ≤ 10 mm
 - ⇒ Macroadenoma: > 10 mm
- According to hormone secretion
 - ⇒ Secretory pituitary adenomas (60%): hormone secretion → hyperpituitarism
 - Lactotroph adenoma: Prolactinoma 35–40%.
 - Somatroph adenoma: Growth hormone (acromegaly) 10–15%.
 Corticotroph: ACTH adenoma (Cushing's disease) 5–10%.

 - Thyrotroph: TSH adenoma <5%
 - ⇒ Non-secretory pituitary adenomas 'chromophobe': Non-functioning 30–35%.
 - Which nonfunctioning pituitary adenoma subtype is characterized by a high recurrence rate, invasion, and increased risk of hemorrhagic infarction?
 - ⇒ Corticotroph adenoma

Prolactinomas are the most common pituitary adenomas

Features: depends on the tumor size and whether the tumor produces hormones

- Secretory microadenomas → hyperpituitarism according to which hormone is secreted
- Secretory macroadenomas → hyperpituitarism + mass effects (e.g., headache, bitemporal hemianopsia, diplopia)
- Non-secretory microadenomas → Asymptomatic
- Non-secretory macroadenomas → Hypopituitarism + mass effects (e.g., headache, bitemporal hemianopsia, diplopia)

Mass effects

- Superior extension → firstly compression of the optic apparatus and later the hypothalamus.
- ⇒ Lateral extension → compression or invasion of the cavernous sinus can compromise third, fourth, or sixth cranial nerve functions, manifest as diplopia in 5 to 15% of pituitary tumour patients.

The presence of an elevated prolactin level along with secondary hypothyroidism and hypogonadism is indicative of stalk compression due to pituitary adenoma

Diagnostics

- Hormone assays
 - ⇒ Basal prolactin levels
 - ⇒ Insulin-like growth factor-1 (IGF-1)
 - ⇒ 24-hour urine cortisol
 - ⇒ Thyroid function tests
- · Cranial contrast MRI (initial test): reveals an intrasellar mass
 - ⇒ CT scan may be considered
- Perimetry: to assess visual field defects

Treatment

- Non-secretory pituitary microadenomas (incidentalomas) → no treatment (only follow-up with serial MRI)
- **Prolactinomas** (PRL is usually >6000mU/ml)
 - ⇒ First-line: dopamine agonists (e.g., cabergoline, bromocriptine) → shrink pituitary adenoma.
 - ⇒ Second-line: trans-sphenoidal hypophysectomy ± adjuvant radiotherapy
- Other pituitary adenomas
 - ⇒ First-line: transsphenoidal hypophysectomy
 - ⇒ Second-line: Medications ± pituitary irradiation

Differentiate between non-functioning adenoma and macroadenoma:

 Although stalk compression with a non-functioning tumour may cause hyperprolactinaemia the concentrations of prolactin are usually below 2000 mU/L and galactorrhoea would be rare.

Except Prolactinomas, all other functioning adenomas are treated primarily by surgery (i.e.; for secondary hyperthyroidism, acromegaly etc).

If the CT scan shows a pituitary tumour with suprasellar extension, which structures is likely to be compressed?

- Optic chiasm
 - ⇒ The optic chiasm lies 5-10 mm above the diaphragm sellae and anterior to the stalk.
 - ⇒ Adenomas > 1.5 cm frequently have suprasellar extension, and the MRI will show compression and upward displacement of the optic chiasm.

Pituitary Incidentaloma

- Asymptomatic, pituitary tumors that are detected on MRI or CT scans done for other reasons without hormonal hyper- or hyposecretion and has a benign natural history.
- The most appropriate strategy →observation and repeat scanning.

Pituitary apoplexy

Sudden-onset retro-orbital headache, vomiting, visual disturbance and hormonal dysfunction should lead you to consider a diagnosis of pituitary apoplexy

Definition

• Sudden hemorrhage into the pituitary gland. Most commonly occurs in patients with a preexisting pituitary adenoma which may be asymptomatic before presentation.

Predisposing factors

pituitary adenomas (most common)

Features

- Features of raised intracranial pressure (↑↑ICP)
 - Sudden-onset retro-orbital headache, similar to that seen in subarachnoid haemorrhage
 - ⇒ vomiting
 - ⇒ **visual disturbance:** diplopia due to pressure on the oculomotor nerves
- Features of pituitary insufficiency
 - ⇒ The main **initial problem** is ↓↓ ACTH, → ↓↓ cortisol → features of an 'Addisonian crisis', i.e. **hypotension**, **hyponatraemia**, hyperkalaemia and hypoglycaemia.
 - ⇒ Subacutely, there can be ⊥ TSH and gonadotropins (LH and FSH).

Diagnosis

· Magnetic resonance imaging

Treatment

- Urgent steroid replacement
- Indications for neurosurgical decompression:
 - ⇒ <u>severe neuro-ophthalmic signs</u> (e.g. severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness)
 - Ocular paresis because of involvement of III, IV or VI cranial nerves in the cavernous sinus in the absence of visual field defects or reduced visual acuity is not an indication for immediate surgery. Resolution will typically occur within days or weeks with conservative management
- Over the long-term → corticosteroid, testosterone and thyroid hormone replacement.

Prognosis

- Nearly 80% of the patients will need some form of hormone replacement after apoplexy.
 - ⇔ Growth hormone deficiency is the most commonly observed deficit after apoplexy and is present in almost all patients but rarely replaced.

Hyperprolactinaemia

The first test to do when seeing anyone with hyperprolactinaemia is to exclude pregnancy, as it is the most common cause.

Prolactin hormone overview

- · Secreted by lactotrophic cells of the anterior pituitary gland
- Effects on females: ↑ breast tissue growth and lactation, ↓ ovulation, ↓GnRH secretion, amenorrhea, galactorrhea, ↓libido
- Effects on males: ↓ spermatogenesis and ↓ libido.
- **Stimulated** by thyrotropin-releasing hormone (TRH)
- Inhibited by hypothalamic dopamine and y-aminobutyric acid (GABA).

Epidemiology

- Hyperprolactinemia is the most common form of hyperpituitarism.
- Post-mortem studies show microadenomas in 10% of the population.
- Microprolactinomas are commoner than macroprolactinomas
- More common in females

Pathophysiology

Prolactin $\to \downarrow$ GNRH $\to \to$ hypogonatrophic hypogonadism (\downarrow LH and FSH $\to \to$ estrogen, \downarrow testosterone)

Which hormones are expected to be low in hyperprolactinaemia?

 Hyperprolactinaemia suppresses the release of gonadotropin-releasing hormone (GRH), which leads to reduced production of luteinising hormone (LH) and follicle-stimulating hormone (FSH).

Causes

Causes of raised prolactin - the Ps

- * pregnancy
- * prolactinoma
- * physiological
- * polycystic ovarian syndrome
- * primary hypothyroidism
- * Phenothiazines, metoclopramide, domperidone
- Physiological: Pregnancy, Sexual intercourse, Nipple stimulation/suckling, Stress.
- Pituitary tumour:
 - ⇒ Prolactinomas. the most common cause (~ 50%) of pathological hyperprolactinemia
 - Microprolactinoma → prolactin level usually of 1,000-3,000 mU/L.
 - Macroprolactinoma: prolactin level usually greater than 3000 mU/L.

- ⇒ Mixed GH/PRL-secreting tumour. Acromegaly (1/3 of patients)
- ⇒ Macroadenoma compressing stalk.
- ⇒ Empty sella.
- Multiple endocrine neoplasia (MEN): Occur in 20% of patients with MEN-1 (prolactinomas are the commonest pituitary tumour in MEN-1). MEN type 1should be considered in presentation with microprolactinoma and recurrent dyspepsia (gastrinomas, insulinomas, carcinoid).
- Hypothalamic disease: mass compressing stalk (craniopharyngioma, meningioma, neurofibromatosis).
- Infiltration: sarcoidosis, Langerhans cell histiocytosis.
- Stalk section: head injury, surgery.
- Cranial irradiation.
- Drug induced: → ↓dopamine release → ↓dopamine inhibition effect on prolactin → ↑
 prolactin release. (Levels less than 1000 are most likely to be drug related)
 - ⇒ Dopamine receptor antagonists (metoclopramide most common, domperidone).
 - ⇒ Neuroleptics (perphenazine, flupentixol, fluphenazine, haloperidol, thioridazine, chlorpromazine, trifluoperazine, risperidone, sulpiride).
 - ⇒ Antidepressants (tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, sulpiride, amisulpride, imipramine, clomipramine, amitriptyline, pargyline, clorgiline).
 - ⇒ Cardiovascular drugs verapamil, methyldopa, reserpine.
 - ⇒ Opiates

 - ⇒ Protease inhibitors e.g. ritonavir, indinavir, zidovudine. Oestrogens. Others—bezafibrate, omeprazole, H2 antagonists.

Metabolic:

- ⇒ Hypothyroidism: TRH increases PRL.
- ⇒ Chronic renal failure: reduced PRL clearance.
- ⇒ Severe liver disease disordered hypothalamic regulation.

Other:

- ⇒ Polycystic ovarian syndrome (PCOS): can make differential diagnosis of menstrual problems difficult.
- ⇒ Chest wall lesions—zoster, burns, trauma (stimulation of suckling reflex).
- ⇒ Temporal lobe seizures, due to close proximity to the hypothalamus.
- No cause found: 'Idiopathic' hyperprolactinaemia.
- Macroprolactinemia ('big' PRL)
 - ⇒ aggregates of prolactin and antibodies (in particular, antiprolactin autoantibodies) that range in size from approximately 150 to 170 kilo Dalton (kD). The most common form of native prolactin in serum is 23 kD in size
 - ⇒ These complexes are immunologically detectable but not biologically active, so they appear to cause no clinical abnormality. Typically, there is hyperprolactinaemia with regular ovulatory menstrual cycles.

- ⇒ Can be misdiagnosed and treated as prolactin hypersecretion
- ⇒ Detection
 - Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin.
 - Gel filtration chromatography (gold standard).

Quetiapine, clozapine, aripiprazole, and olanzapine are antipsychotics, with little or no effect on prolactin (lower binding affinity to D2 receptors).

Cranial irradiation may initially cause hyperprolactinaemia but a low PRL is typical after a year.

A patient presented with **elevated oestradiol** and **prolactin** with suppressed (LH/FSH) and recent amenorrhoea. **what is the most likely diagnosis?**

Pregnancy

Features of excess prolactin

- Hyperprolactinaemia (microadenomas and macroadenomas)
 - ⇒ Men: impotence, loss of libido, erectile dysfunction, rarely galactorrhoea
 - ⇒ Women: amenorrhoea, galactorrhoea, reduced libido
- Mass effects (macroadenomas only):
 - ⇒ Headaches and visual field defects (uni- or bitemporal field defects).
 - ⇒ Hypopituitarism.
 - ⇒ Invasion of the cavernous sinus may lead to cranial nerve palsies.
- Long-term risk of d JBMD.

Investigations

- Serum prolactin (PRL)
 - ⇒ stress of venepuncture may cause mild hyperprolactinaemia, so **2–3 levels should be checked**, preferably through an indwelling cannula after 30min
 - ⇒ Serum PRL <2,000mU/L is suggestive of a microprolactinoma or a non-functioning macroadenoma compressing the pituitary stalk.
 - ⇒ Serum PRL >4,000mU/L is diagnostic of a macroprolactinoma.
 - ⇒ Hook effect:
 - Very high prolactin concentrations can interfere with immunoassay systems
 resulting in falsely low prolactin determination. this is due to "hook effect" which
 describes the inhibition of immune complex formation by excess antigen
 concentrations.
 - this is an important consideration in patients with large pituitary adenomas when the clinical suspicion of prolactinoma is strong, as in patients with amenorrhoeagalactorrhoea or longstanding hypogonadism.
 - appropriate dilution of the serum in such cases helps in accurate estimation of serum prolactin concentration.
- **Thyroid function and renal function:** Hypothyroidism and chronic renal failure are causes of hyperprolactinaemia.
- MRI of the brain: the most accurate diagnostic test. Be aware MRIs do not rule out small microadenomas.

Levels of prolactin

- < 1000 → drug-induced prolactinaemia
- 1000 -- 3000 mU/l → microprolactinoma.
- > 3000 → macroprolactinoma.

Treatment of prolactinomas

Dopamine agonists (e.g. cabergoline, bromocriptine) are first-line treatment for prolactinomas, even if there are significant neurological complications

- Dopamine agonist (DA) (Cabergoline and Bromocriptine)
 - Dopamine agonists are first-line treatment for prolactinomas, even if there are significant neurological complications
 - ⇒ they are able to normalize the prolactin levels, restore gonadal function and reduce tumor size
 - ⇒ A meta-analysis suggested that cabergoline is more efficacious than bromocriptine in normalising prolactin and has a better side effect profile and is therefore the treatment of choice.
 - ⇒ If patient is asymptomatic, there is no absolute requirement for treatment.
 - ⇒ Side effects:
 - Both pergolide and cabergoline may be associated with pericarditis, cardiac valve regurgitation, pericardial effusion and pulmonary hypertension.
 - Ropinirole may be an appropriate alternative in this case, otherwise surgery
 would be the next most appropriate step.
 - Although cabergoline in higher doses used for Parkinson's disease can cause right-sided cardiac fibrosis, there is no evidence for this using the lower doses necessary for the control of PRL levels.
 - **⇒** Contraindications
 - cardiac valve fibrosis
 - pulmonary fibrosis.
- Pituitary surgery
 - ⇒ rarely required in prolactinomas and is generally reserved for patients intolerant of or resistant to dopamine agonist therapy.
- Radiotherapy can be used to reduce the chance of tumour recurrence, but is rarely required.

Prolactinomas in pregnancy

- Risk of pregnancy
 - ⇒ The main concern for the mother is adenoma growth with potential mass effect and visual loss
 - ⇒ The risk of tumor enlargement during pregnancy is found to depend on tumor size:
 - 3% for microprolactinomas
 - 32% for macroprolactinomas that were not previously operated on
- Before pregnancy: For women with macroadenomas
 - ⇒ 1st line: dopamine agonist
 - ⇒ 2nd line (if size does not decrease): transsphenoidal surgery
 - ⇒ pregnancy is not recommended in women with <u>drug resistant large</u>
 <u>macro</u>prolactinomas and they should not conceive even if the tumor is intrasellar,
 until the size is reduced by transsphenoidal surgery.

During pregnancy

- If possible, stop dopamine agonists as soon as the pregnancy is confirmed except in: invasive macroprolactinomas or pressure symptoms.
 - There is no evidence that DA is teratogenic, but <u>Once pregnancy is established</u>, <u>DA is not necessarily required</u>, and so most physicians recommend stopping it for the duration.
 - It is clearly not needed to treat hypogonadism and it is not needed to control size of adenoma as microprolactinomas almost never spontaneously increase in size.
- ⇒ In case the patient becomes symptomatic with visual disturbance or progressive headaches, an MRI without gadolinium (not a CT) should be performed to assess changes in tumor size.
- ⇒ evidence of macroadenoma growth on MRI; performed for severe headaches or visual field abnormalities) → cabergoline or bromocriptine
- ➡ If treatment is required bromocriptine has the most safety data (the first drug of choice in symptomatic pregnant). Cabergoline may be considered if the adenoma does not respond to bromocriptine

Breastfeeding

- ⇒ Asymptomatic: Breastfeeding is not contraindicated, but dopamine agonists should not be used, because they impair lactation.
- ⇒ woman who has visual field impairment: should not breastfeed and should be treated with a dopamine agonist

Cabergoline VS Bromocriptine

Comparison	Cabergoline	Bromocriptine
Dopamine receptors	D2 selectively	D2 and other dopamine receptors
	long acting (once or twice weekly → better tolerability and patient compliance)	Short acting (requires multiple doses per day)
Effectiveness in lowering the prolactin	More effective in lowering the prolactin	Less effective
Safety during pregnancy	Less data about safety	Less teratogenicity than cabergoline

Thyroid and parathyroid conditions

Physiological effects of thyroid hormones

Thyroid hormones production

- The thyroid utilises tyrosine and iodine to manufacture thyroxine and T3.
- lodide is taken into the thyroid follicular cells by active transporters and then oxidised to iodine by thyroid peroxidase.
- Organification occurs when iodine is attached to tyrosine molecules which themselves are attached to thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of 2 molecules of DIT forms thyroxine.
- Maternal TRH readily crosses the placenta; maternal TSH and T4 do not.
- An enzyme called 5'-deiodinase in the blood removes an iodine molecule to convert T4 to the biologically active T3. So T4 can be considered a prohormone: it must be

converted to T3 to exert any of its effects on the body. This conversion occurs throughout the body. In contrast, T4 can only be produced in the thyroid.

- Peripheral metabolism of thyroxine is the most common source of T3.
- Peripheral conversion is inhibited by glucocorticoids, β-blockers, and propylthiouracil(PTU)
- T4 is much more abundant than T3 in the bloodstream. T3 is more biologically active than T4.
- T3 has a much shorter half-life. T3 is more readily broken down by 5'-deiodinase.
- The half-life of T3 is about one day (~ 20 hours), whereas the half-life of T4 is about one
 week (~ 190 hours). This longer half-life makes T4 suitable for use as a depot form that
 can be used replacement therapy.
- Thyroid peroxidase first oxidizes iodide to iodine. Then, it attaches iodine to thyroglobulin.
 Then, it combines monoiodotyrosine (MIT) and diiodotyrosine (DIT) or two molecules of DIT
 to make T3 and T4, respectively.
- Excess iodide inhibits thyroid peroxidase. This is called the Wolff-Chaikoff effect.

Thyroid binding globulin (TBG)

- In the blood, more than 99% of T3 and T4 are bound to thyroid binding globulin (TBG) and thus not biologically active. The small unbound is called free T3 and T4. This is the biologically active form.
- TBG levels are increased during pregnancy and with oral contraceptive use because estrogen promotes liver TBG synthesis. In these patients, bound and total thyroid hormones are elevated while free T3 and T4 remain normal.

Causes of altered concentration of TBG

• ↑TBG	• ↓TBG
 Pregnancy 	 Androgens
 OCP and other sources of 	 Large doses of glucocorticoids
oestrogens	 Cushing's syndrome
 Tamoxifen 	 Chronic liver disease
 Hepatitis A; chronic active hepatitis 	 Severe systemic illness
 Biliary cirrhosis 	 Active acromegaly
 Acute intermittent porphyria 	 Nephrotic syndrome
 Newborn state 	 Genetically determined
 Genetically determined 	 Drugs, e.g. phenytoin
·	 Factitious thyrotoxicosis

Thyroid hormone receptors

- The thyroid hormone receptor is a nuclear receptor.
- The action of T3 requires entry into the nucleus, where the thyroid hormone receptors are found in cells throughout the body.
- . The TRH receptor uses the Gq pathway, while the TSH receptor uses the Gs pathway.

Regulations

- TRH binds to a Gq receptor on anterior pituitary tissue → activate membrane-bound
 phospholipase C →↑ inositol triphosphate (IP3) →↑intracellular calcium → activates
 protein kinase C →↑release of TSH.
- TSH binds to a Gs receptor on thyroid gland tissue → activate adenylate cyclase →
 promotes conversion of ATP to cAMP, which acts as a second messenger →↑synthesis
 and secretion of T3/T4.

Functions of thyroid hormones: 7 B s

- Brain maturation
- Bone growth (synergism with GH)
- β-adrenergic effects. β1receptors in heart CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis
- Basal metabolic rate (via Na+/ K+ ATPase O2 consumption, RR ,body temperature)
- Blood sugar (glycogenolysis, gluconeogenesis) (Enhance insulin sensitivity)
- Break down lipids (lipolysis)
- Stimulates surfactant synthesis in Babies

What is the defect Which responsible for thyroid hormone dyshormonogenesis?

⇒ Defect in iodine organification

Thyrotropin is a glycoprotein hormone (glycosylated)

Calcitonin

Overview

- Polypeptide hormone
- Produced by the parafollicular cells (also known as C-cells) of the thyroid,

Calcitonin receptor

- found on osteoclasts, and in the kidney and regions of the brain,
- is a G protein-coupled receptor, which is coupled by G_s to adenylate cyclase and thereby to the generation of cAMP in target cells.
- It may also affect the ovaries in women and the testes in men.

Action

- \$\times\$ bone resorption. Reduce blood calcium (Ca²⁺), opposing the effects of parathyroid hormone (PTH).
- Calcitonin-gene related peptide causes vasodilatation.
- · Calcitonin lowers blood Ca2+ levels in two ways:
 - 1. Major effect: Inhibits osteoclast activity in bones
 - Minor effect: Inhibits renal tubular cell reabsorption of Ca2+ and phosphate, allowing them to be excreted in the urine

Regulation

- · Secretion of calcitonin is stimulated by:
 - ⇒ ↑serum [Ca2+]
 - ⇒ gastrin and pentagastrin.

Calcitonin escape phenomenon

- Despite high serum calcitonin levels, which mechanism best explains the normal calcium levels in a patient with thyroid nodule?
 - ⇒ High levels of calcitonin down regulates its receptor
 - Calcitonin's primary function is to act on osteoclasts and decrease serum calcium levels.
 - Huge amounts of calcitonin are secreted in medullary carcinoma of the thyroid, or when calcitonin is used therapeutically to treat certain medical conditions, such as Paget's disease, osteoporosis, and hypercalcemia. Its effects on

- osteoclasts disappear after one week of therapy. This is called the 'calcitonin escape phenomenon'.
- The biochemical basis for the 'calcitonin escape phenomenon' is the down regulation of its receptor.
- Whenever the levels of calcitonin become high, they down regulate the receptor by rapid and prolonged down regulation of calcitonin receptor messenger RNA.

To remember that calcitonin keeps the calcium in the bones, think: Calci-bone-in!

Hypothyroidism

Epidemiology

- Affects around 1-2% of women in the UK
- Around 5-10 times more common in females than males.

Causes

- Hashimoto's thyroiditis
 - ⇒ Autoimmune disease, Associated with HLA-DR3
 - ⇒ Most common cause
 - ⇒ 10 times more common in women
 - ⇒ May cause transient thyrotoxicosis in the acute phase
 - <u>Early in the course of disease</u>, T4 and TSH levels are normal and there are high levels of thyroid peroxidase antibodies and, less commonly, antithyroglobulin antibodies.
 - Thyroid radioiodine uptake may be increased because of defective iodide organification, together with a gland that continues to trap iodine.
 - ⇒ Associated with
 - Other autoimmune diseases: IDDM, Addison's, pernicious anaemia, coeliac disease.
 - Turner's syndrome, Down's syndrome
 - Thyroid lymphoma
 - **⇒** Features
 - Features of hypothyroidism (eg hair loss, hoarse voice and periorbital oedema)
 - Goitre: firm, non-tender
 - Antibodies
 - anti-thyroid peroxidase (anti TPO) also known as (Anti-microsomal antibodies)
 - anti-thyroglobulin antibodies (anti-Tg)
- Dietary iodine deficiency
 - ⇒ Common in parts of central Africa, where the diet is poor in iodine and access to sea fish is relatively difficult. Uncommon in the developed world.
 - ⇒ Iodine daily requirement: according to WHO recommendations
 - Age >12 and adults → 150 microgram
 - Pregnant and lactating women → 200 microgram
 - ⇒ It may present as goitre without hypothyroidism, or in severe cases can progress to frank hypothyroidism.
 - ⇒ Urinary iodide excretion is the next investigation to establish the diagnosis
 - As more than 95% of dietary iodide is excreted in urine, a 24 hour urinary excretion of iodide is an excellent index of dietary iodine intake and can unmask an iodide deficiency state.

- Postpartum thyroiditis (subacute lymphocytic thyroiditis)
- De Quervain's thyroiditis (subacute granulomatous thyroiditis)
- · Riedel thyroiditis: a dense fibrosis that replaces normal thyroid parenchyma
- latrogenic: after treatment of hyperthyroidism with anti-thyroid drugs, thyroidectomy or radioiodine.
- Drug- induced
 - ⇒ Amiodarone
 - \Rightarrow Lithium \rightarrow **goitre** in up to **40%** and **hypothyroidism** in about **20%**.
- Secondary (central) hypothyroidism (rare):
 - ⇒ TSH is not appropriately elevated inspite of low T4.
 - \Rightarrow pituitary disorders $\rightarrow \downarrow$ TSH levels $\rightarrow \downarrow$ T3/T4 levels
- Tertiary hypothyroidism: hypothalamic disorders → ↓ TRH → ↓ TSH → ↓ T3/T4 levels

Hashimoto's thyroiditis = Hypothyroidism + Goitre + Anti-TPO

Hashimoto's thyroiditis is associated with thyroid lymphoma

Features

- Symptoms related to decreased metabolic rate
 - ⇒ Fatigue, decreased physical activity
 - ⇔ Cold intolerance
 - ⇒ Hair loss, brittle nails, and cold, dry skin
 - ⇒ Weight gain (despite poor appetite)
 - ⇒ Hypothyroid myopathy
 - ⇒ Woltman sign: a delayed relaxation of the deep tendon reflexes
 - ⇒ Entrapment syndromes (e.g., carpal tunnel syndrome)
- Symptoms related to decreased sympathetic activity
 - ⇒ Decreased sweating
 - ⇒ Cold skin (due to decreased blood flow)
 - ⇒ Constipation (due to decreased gastrointestinal motility)
 - ⇒ Bradycardia
- Symptoms related to generalized myxedema
 - ⇒ puffy appearance
 - ⇒ Myxedematous heart disease (dilated cardiomyopathy, bradycardia, dyspnea)
 - ⇒ Hoarse voice, difficulty articulating words
 - ⇒ Pretibial and periorbital edema: due to accumulation of glycosaminoglycans and hyaluronic acid within the reticular layer of the dermis. complex protein mucopolysaccharides bind water → nonpitting edema
- · Symptoms of hyperprolactinemia
 - Abnormal menstrual cycle; secondary amenorrhea; menorrhagia
 - ⇒ Galactorrhea
 - ⇒ Decreased libido, erectile dysfunction, delayed ejaculation, and infertility in men
- Further symptoms
 - ⇒ Impaired cognition; somnolence, depression

Investigations

- Thyroid function tests
 - TSH: Best initial screening test. Normal TSH levels generally rule out primary hypothyroidism and hyperthyroidism
 - ⇒ FT4
- Anti-TPO antibodies
 - ⇒ present in 10% females without thyroid pathology

Associated laboratory manifestations

- **Euvolaemic hyponatraemia** often resulting from inappropriate production of antidiuretic hormone.
- Creatine kinase: increased in hypothyroid myopathy
- Macrocytic anemia
- Glucose intolerance
- Dyslipidaemia
 - ⇒ ↓thyroid hormones → ↓ use of glucose and FFAs as fuel → hyperlipidemia and glucose intolerance.
 - ⇒ The predominant lipid picture in hypothyroidism is mixed dyslipidaemia (↑LDL , ↑ triglycerides)
 - ⇒ may well resolve following the appropriate replacement with thyroxine.
 - ⇒ Hypothyroidism is a risk factor for statin induced myopathy, therefore before increase statin dose it is important to correct thyroid profile
- **Slightly raised bilirubin:** In hypothyroidism, the activity of bilirubin UDP-glucuronyl transferase is decreased, resulting in a reduction in bilirubin excretion.
- Hyperprolactinemia → Hyperprolactin (hyperPRL) hypogonadism
 - ⇒ Hypothyroidism→ ↑↑TRH (thyrotropin-releasing factor) → act as prolactin-releasing factor→ release of prolactin and hyperprolactinaemia.
- Hypercarotenaemia (high blood levels of beta-carotene) → yellowing of the skin (xanthoderma).
- Clinically silent pericardial effusion is common in untreated hypothyroidism (Pericardial or pleural effusions)

Anti-TPO antibodies are present in 10% females without thyroid pathology

Thyrotropin is a glycoprotein hormone (glycosylated)

If the thyroid peroxidase (TPO) antibodies during early gestation are strongly positive. What is the chance of developing hypothyroidism in the post-partum period? $\rightarrow 50\%$

Management

- Levothyroxine: BNF recommends the initial starting dose as following:
 - ⇒ For patients with cardiac disease, or patients over 50 years: 25mcg od with dose slowly titrated.
 - ⇒ For other patients: 50-100mcg od
- Follow-up: following a change in thyroxine dose TFT should be checked after 8-12 weeks
- Target: TSH value 0.5-2.5 mU/l.

If you made a diagnosis of Hashimoto's, what is the next best step in the management?

Rule out Addison's, short synacthen test even if the sodium is normal. Addison's may
coexist with Hashimoto's, masked by the hypothyroid. Treating hypothyroid will unmask the
Addison's and precipitate adrenal crisis.

Monitoring

Monitoring of thyroid status

Thyroid-stimulating hormone (TSH) is the most sensitive indicator of thyroid status.

- Normal TSH result suggests → adequate thyroxin replacement & euthyroidism
- ↑↑ (TSH) with normal (T4) suggest → poor compliance
- ↓↓ (TSH) with normal high (T4) suggests → over-replacement

Causes of persistently elevated TSH levels despite adequate thyroxine therapy:

- Compliance (the commonest cause)
- Drugs interaction such as:
 - ⇒ rifampicin
 - ⇒ calcium supplements (e.g. calcium carbonate)
 - ⇒ Amiodarone
 - ⇒ **ferrous sulphate** (give at least 2 hours apart)
 - ⇒ Omeprazole,
 - ⇒ Hormone replacement therapy (HRT) → ↑ thyroid binding proteins → ↓ free thyroid hormone → requiring an increase in thyroxine dose.
 - ⇒ Treatment with estrogens may necessitate a dose increase.
 - ⇒ Glucocorticoids interfere with thyroid hormone metabolism and the dose of levothyroxine may need to be reduced.
- · Malabsorption syndromes like coeliac disease
- Nephrotic syndrome

Iron reduces the absorption of thyroxine

Complications

- Myxedema coma
 - ⇒ Definition: potentially life-threatening decompensation. usually occurs in the elderly who are typically non-compliant.
 - ⇒ **Features**: impaired mental status; hypothermia; bradycardia, myxedema
 - **⇒** Treatment:
 - Intravenous thyroid hormones : levothyroxine ; PLUS liothyronine
 - Treatment with hydrocortisone is recommended until Addison's disease can be excluded, as just giving thyroid hormone alone may precipitate an adrenal crisis.
 - rewarming.

Primary thyroid lymphoma

- ⇒ Hashimoto thyroiditis is the most common cause of hypothyroidism and the only known risk factor for primary thyroid lymphoma.
- ⇒ Almost all primary thyroid lymphomas are non-Hodgkin large B-cell lymphomas.
- Hashimoto's encephalopathy
 - ⇒ Extremely rare
 - ⇒ Considered to be part of an autoimmune encephalitis.
 - ⇒ Often, the condition presents prior to the development of hypothyroidism and patients can be entirely euthyroid yet with quite profound neurological dysfunction.
 - ⇒ Result in altered mental state, myoclonus and ataxia.
 - ⇒ Should be suspected in TSH derangement however there may be no clinical evidence of thyroid dysfunction.
 - ⇒ The next laboratory tests should be → Anti-thyroid peroxidase antibodies
 - ⇒ It is a steroid responsive encephalopathy

A history of an acutely painful, left-sided goitre in euthyroid and apyrexial patient with normal labs and no prior history of thyroid disease ?

Haemorrhage into a cyst

Pendred's syndrome

signs of deafness and hypothyroidism → Pendred's syndrome

Definition

- Pendred syndrome is an autosomal recessive disorder that results in the reduced activity of pendrin.
- Pendrin is importance for:
 - \Rightarrow lodide transport in the thyroid gland: defect \rightarrow hypothyroidism with goiter.
 - ⇒ Electrolyte homeostasis in the inner ear: defect → sensorineural hearing loss
 - ⇒ Maintain sodium chloride balance in the distal nephron: defect → if treated with a thiazide diuretic that inhibits NCC, severe hypovolemia and metabolic alkalosis develop.

Features

- · Hypothyroidism with goiter
- Sensorineural deafness
- Hypovolemia and metabolic alkalosis in response to thiazide diuretics.

Diagnosis

- genetic testing (Pendred's syndrome (PDS) gene, chromosome 7), (SLC26A4)
- audiometry and MRI imaging to look for characteristic one and a half turns in the cochlea, compared to the normal two and a half turns.

Treatment

- thyroid hormone replacement
- · cochlear implants.

Riedel's thyroiditis

Definition

 A chronic autoinflammatory disease, characterized by conversion of regular thyroid parenchyma to diffuse fibrous growth that may extend into the surrounding tissue.

Features

- Typically presents as a painless, hard, solid thyroid enlargement (described as stony or woody.)
- Extension beyond the thyroid differentiates this from the fibrosing variant of Hashimoto thyroiditis.
- Associated hypothyroidism (although most patients are euthyroid), absence of cervical adenopathy and slow course are differentiate this from anaplastic thyroid cancer.
- Complications → Fibrotic invasion of adjacent anatomic structures (e.g. Hypoparathyroidism)

Diagnosis

- Open surgical biopsy is essential for the correct diagnosis.
- IgG4 levels are elevated in over 95% of cases.

Treatment

- Steroids and tamoxifen to inhibit connective tissue proliferation.
- wedge resection of the thyroid isthmus to alleviate tracheal obstruction is still the preferred surgical therapy

Sick euthyroid syndrome

Definition

- A decrease in thyroid hormone levels that occurs in severe illness despite normal thyroid gland function.
- Now referred to as non-thyroidal illness.

Pathology

• Increase in 5¹ deiodinase Type 3 levels

Causes

- Any sever ill ness disease or organ failure
- Common in intensive care patients

Feature

- Low T4 and T3.
- TSH are typically low, but may be low-normal or normal.

Management

- Changes are reversible upon recovery from the systemic illness.
- the most appropriate next step in management → repeat thyroid function tests in 3 months

Subclinical hypothyroidism

Subclinical hypothyroidism in a patient younger than 70:

- TSH > 10mU/l → Start levothyroxine replacement
- TSH 4-10mU/I \rightarrow repeat the test in six months.

Diagnosis

TSH levels above the range but with normal levels of thyroxine (T4) and triiodothyronine (T3).

Epidemiology

- found in 8–10% of the population,
- more common in young women and increases with age.

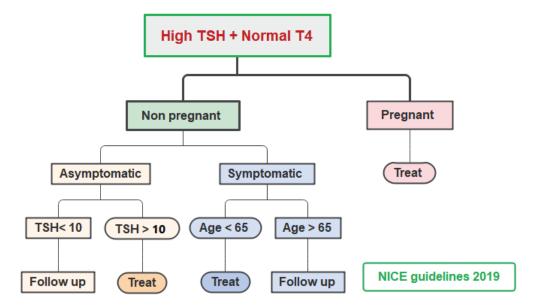
Significance

· may be associated with an increased risk of cardiovascular disease

- Adverse pregnancy outcome: \(\)risk of severe preeclampsia, placental abruption, preterm birth
 - ⇒ subclinical hypothyroidism with positive anti-thyroid peroxidase (TPO) antibodies tend to have the highest risk of adverse pregnancy outcomes

Indications for treatment

- TSH > 10
- Hypothyroid symptoms (regardless TSH level)
- Pregnancy or pregnancy planned in the near future



Management

- TSH is between 4 10mU/L (on 2 separate occasions 3 months apart).
 - ⇒ If symptomatic
 - < 65 years:</p>
 - give a 6-month trial of levothyroxine
 - ❖ If there is no improvement in symptoms, stop levothyroxine
 - In older people (especially > 80 years) →follow a 'watch and wait' strategy, generally avoiding hormonal treatment'
 - ⇒ If asymptomatic → observe and repeat thyroid function in 6 months
- TSH is > 10mU/L (on 2 separate occasions 3 months apart) →start treatment (even if asymptomatic)

Monitoring

- Monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment
 - ⇒ With features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies → once a year
 - ⇒ Without features suggesting underlying thyroid disease → once every 2 to 3 years.

Abnormal thyroid function

Abnormal thyroid function tests

Test	Possible cause	
High TSH + low free T4	Primary hypothyroidism	
Low TSH + elevated free T4 and free T3	Primary hyperthyroidism	
Low or normal TSH + low T4	Secondary hypothyroidism	
Low TSH and normal free T4	T3 toxicosis (approximately 5% of thyrotoxicosis)	
Low TSH and normal free T4 and free T3	 Subclinical hyperthyroidism Recovery from thyrotoxicosis Excess thyroxine replacement Non-thyroidal illness 	
High TSH and high free T4 and free T3	 TSH-secreting pituitary tumour (2ry hyperthyroidism) Thyroid hormone resistance Heterophile antibodies, leading to spurious measurements of free T4 and free T3 Thyroxine replacement therapy (including poor compliance) 	
High TSH and Normal free T4	Poor compliance with thyroxine Subclinical hypothyroidism	
High free T4 and low normal free T3, normal TSH	Amiodarone	
Low or normal TSH and low normal free T4 and free T3	Non-thyroidal illnessCentral hypothyroidismIsolated TSH deficiency	
Normal TSH and low free T4	Steroid therapy	
Low TSH and low free T4	Sick euthyroid syndrome (non-thyroidal illness)	

Post-partum thyroiditis

Definition

• thyroid dysfunction occurring within the first 6 months after delivery.

Course of disease

 Hyperthyroid status followed by a hypothyroid phase at three to six months, followed by spontaneous recovery in one third of cases. In the remaining two-thirds, a single-phase pattern or the reverse occurs.

Features

 characteristic sequence of three phases: hyperthyroidism, followed by hypothyroidism, and then recovery

Pathophysiology

 The exact aetiology is unknown but lymphocytic infiltration of the thyroid is typical, suggesting auto-immunity.

Prevalence

• occurs in approximately 5-7% of females

Risk factors

- Common in whom thyroid peroxidase (TPO) antibodies were positive prior to delivery
- twice common in patients with type 1 diabetes mellitus.

Investigations

• Thyroid peroxidase (TPO) antibodies are found in 90% of patients

Management

- the thyrotoxic phase is not usually treated with anti-thyroid drugs as the thyroid is not
 overactive.
 - ⇒ Symptomatic treatment using → beta-blockers for relief of tremor or anxiety.
 - Propranolol is typically used for symptom control
- the hypothyroid phase is usually treated with thyroxine
 - ⇒ withdrawal period after 6 months to measure recovery of thyroid function.
 - ⇒ Stop thyroxine and reassess thyroid function in approximately one month.

Prognosis

- Recurrence of thyroiditis is common in subsequent pregnancies
- in up to 40% permanent hypothyroidism develops.

Subacute (De Quervain's) thyroiditis

Thyrotoxicosis with tender goitre = Subacute thyroiditis (De Quervain's thyroiditis)

Basics

- Subacute thyroiditis also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis
- It is associated with HLA-B35

Pathophysiology

- Occur after viral infection
- thyroid inflammation drives increased release of stored thyroid hormone, rather than the clinical picture being due to overproduction of T3 and T4.

Features

Tender goitre, hyperthyroidism and raised ESR + globally reduced uptake on technetium thyroid scan is typical (De Quervian)

- typically presents with hyperthyroidism symptoms
 - ⇒ triphasic course of transient thyrotoxicosis, followed by hypothyroidism, followed by a return to euthyroidism.
 - ⇒ The thyrotoxic phase is due to thyroid follicular damage and release of preformed hormone
- painful goitre.
 - ⇒ The thyroid enlargement is typically rapid, occurring over a period of days.
 - ⇒ The thyroid gland will be <u>firm</u>, <u>enlarged</u> bilaterally or unilaterally <u>due to extravasation</u> of colloid from the follicles causing a <u>granulomatous reaction</u>.
- raised temperature (e.g. flu-like symptoms)

Investigations

- Hyperthyroidism
 - ⇒ As the condition resolves patients become hypothyroid and then euthyroid.
- raised ESR (>50 and usually 100), elevated CRP.
- Thyroid ultrasound: shows
 - areas of hypoechoic echotexture
 - decreased or normal vascular flow by Doppler.

- thyroid scintigraphy: globally reduced uptake on iodine-131 scan
 - ⇒ the most helpful investigation in establishing the diagnosis → Radioactive iodine uptake scan
 - ⇒ Radioiodine uptake is typically less than 1% at 24 hours (Tc 99m uptake is similarly low).

Management

- usually self-limiting most patients do not require treatment
- · symptomatic control.
 - ⇒ Symptoms of hyperthyroidism:
 - should be managed with beta blockade as required.
 - no role for thionamides.
 - ⇒ thyroid pain may respond to aspirin or other NSAIDs
- steroids (Prednisolone)
 - ⇒ in more severe cases, particularly if hypothyroidism develops

Prognosis

- The hypothyroidism is usually mild but persists for 2 4 months.
- return to normal thyroid function in >90% of patients
- A few patients (~5%) remain hypothyroid and need long-term thyroid hormone replacement.
- · Recurrences are uncommon.

In De Quervain's thyroiditis, treatment is aimed at reducing inflammation with NSAIDS or steroids in severe cases (e.g. prednisolone 20–40 mg/day for two weeks and titrated down).

Subclinical hyperthyroidism

Patient with subclinical hyperthyroidism with measurable TSH and no features of exogenous thyroid dysfunction can be managed conservatively

Subclinical hyperthyroidism: normal FT4 and FT3 with a suppressed TSH level with non-specific symptoms

T3 levels should be performed where tests show normal T4 with suppressed TSH

Definition

- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually < 0.1 mu/l)

Causes

- usually occurs in the setting of thyroid overactivity due to Graves' disease or autonomously functioning thyroid nodules sufficient to suppress pituitary TSH secretion but insufficient to cause an elevation of circulating hormones.
- multinodular goitre, particularly in elderly females
- · excessive thyroxine may give a similar biochemical picture

Complications

- Cardiovascular (atrial fibrillation)
- Bone metabolism (osteoporosis)
- · impact on quality of life
- · increase the likelihood of dementia

Management

- Observation
 - ⇒ Repeat measurement of TSH (with serum FT4 and FT3)
 - ⇒ TSH levels often revert to normal therefore levels must be persistently low to warrant intervention
- therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission
- indication for definitive therapy:
 - ⇒ presence of an unmeasurable TSH (sustained TSH suppression (<0.1 mU/l)) and/or
 - ⇒ exogenous thyroid dysfunction
 - symptoms of hyperthyroidism,
 - osteoporosis
 - a DEXA scan is appropriate next line management to quantify the osteoporosis risk and inform the decision as to whether or not to treat the sub-clinical hyperthyroidism.
 - atrial fibrillation, or
 - unexplained weight loss
 - ⇒ The American Association of Clinical Endocrinologists recommends that treatment is considered in patients with a <u>persistently low TSH</u> level if they are <u>older than 65</u> years or are at risk of osteoporosis or heart disease.

Prognosis

Progression to overt hyperthyroidism occurs in 1-3 % of elderly patients per year.

Thyrotoxicosis

The PTH level in primary hyperparathyroidism may be normal

Causes

- Graves' disease (50-60% of cases of thyrotoxicosis)
- · Toxic nodular goitre
- Toxic adenoma (Plummer's disease)
- Thyroiditis
 - ⇒ Subacute granulomatous thyroiditis (de Quervain thyroiditis)
 - ⇒ Subacute lymphocytic thyroiditis (e.g., postpartum thyroiditis)
- Acute phase of Hashimoto's thyroiditis (Hashitoxicosis): later results in hypothyroidism.
 - Transient thyrotoxicosis in patients with early Hashimoto's disease resulting from the initial destruction of the thyroid gland and subsequent release of thyroid hormones.
 - 2. Positive thyroid peroxidase antibodies and negative TSH receptor antibody
- Amiodarone therapy
- β-hCG-mediated hyperthyroidism (hydatidiform mole, choriocarcinoma)
- Secondary thyrotoxicosis: thyrotoxic with an abnormally 'normal' TSH.
 - ⇒ TSH-producing pituitary adenoma
 - Ectopic TSH (e.g. struma ovarii, ovarian teratomas can produce exogenous TSH causes secondary hyperthyroidism. can be visualized with a pelvic ultrasound or abdominal CT.)
 - Negative neck ultrasound and neck exam in the setting of hyperthyroidism and low radioiodine uptake.

- Factitious hyperthyroidism: Exogenous thyrotoxicosis, diagnosed by:
 - Undetectable thyroglobulin (a precursor of thyroid hormones, indicates an external source of thyroid hormone)
 - ⇒ Radioactive uptake thyroid scan
 - endogenous causes of thyrotoxicosis → increased radioactive uptake
 - In thyrotoxicosis factitia, uptake is globally reduced.
- T3 thyrotoxicosis
 - ⇒ associated with 5% of cases of thyrotoxicosis.
 - ⇒ suppressed TSH, low or normal T4 and fT4, high fT3
- Excess iodine ingestion
 - ⇒ Kelp is a very rich source of iodine. Treatment is withdrawal of the kelp with monitoring of thyroid function.

lodine excess

- Jod-Basedow phenomenon:
 - ⇒ **Hyperthyroidism following iodine excess** (e.g., after IV contrast administration, due to intake of amiodarone or other iodine-containing drugs, etc.)
 - ➡ Mechanism: occurs due to either overactivation of the entire thyroid gland or, more commonly, autonomous nodules within the gland after iodine repletion without adequate feedback control from the pituitary gland.
- · Wolff-Chaikoff effect
 - Hypothyroidism following iodine excess (opposite effect to Jod-Basedow phenomenon)
 - → Mechanism: excess iodine inhibits thyroid peroxidase → decreases T3/T4 production

Thyrotoxicosis factitia (thyroxin abuse): The combination of low thyroglobulin, decreased uptake on scintigraphy and raised T4

T3 thyrotoxicosis should always be considered in patients with suppressed TSH and normal T4 levels, especially when patients are symptomatic.

Feature

- General
 - ⇒ Heat intolerance
 - ⇒ Excessive sweating because of increased cutaneous blood flow
 - ⇒ Weight loss despite increased appetite
 - ⇒ Frequent bowel movements (because of intestinal hypermotility)
 - ⇒ Weakness, fatigue
 - ⇒ Onycholysis: a separation of the nail from the nail bed.
 - ⇒ Infiltrative dermopathy, especially in the pretibial area (pretibial myxedema)
- Goiter: Diffuse, smooth, nontender goiter; often audible bruit
- Eyes
 - ⇒ Lid lag: caused by adrenergic overactivity, which results in spasming of the smooth muscle of the levator palpebrae superioris
 - ⇒ Lid retraction: "staring look"
 - ⇒ Lid retraction and lag are signs of sympathetic overactivity, and <u>occur in any</u> thyrotoxic state (thyroxine potentiates the action of catecholamines).
 - ⇒ Graves ophthalmopathy (exophthalmos, edema of the periorbital tissue)

Decreased libido

- Cardiovascular
 - ⇒ Palpitations, tachycardia, irregular pulse (due to atrial fibrillation/ectopic beats)
 - caused by increased beta-adrenergic tone.
 - Atrial fibrillation (AF) occurs in 10% to 25% of patients with hyperthyroidism
 - ⇒ Hypertension with widened pulse pressure
 - Systolic pressure is increased due to increased heart rate and cardiac output.
 - Diastolic pressure is decreased due to decreased peripheral vascular resistance.
- Endocrinological
 - ⇒ Female: oligo/amenorrhoea, anovulatory infertility, dysfunctional uterine bleeding
 - ⇒ Male: gynecomastia, decreased libido, infertility, erectile dysfunction
- Musculoskeletal
 - ⇒ Fine tremor of the outstretched fingers
 - ⇒ Hyperthyroid myopathy: Typically affects proximal muscles (e.g., hip flexors, quadriceps) more than distal muscles. Serum creatine kinase levels are most often normal
 - ⇒ Osteopathy: osteoporosis due to the direct effect of T3 on osteoclastic bone resorption
- Neuropsychiatric
 - ⇒ Anxiety, Restlessness, Insomnia
 - ⇒ Hyperreflexia

Investigations

- Thyroid function tests: low TSH, plus high T4 and T3.
 - ⇒ The most sensitive test to diagnosis hyperthyroidism is TSH level (initial screening test).
 - ⇒ In primary hyperthyroidism the TSH should always be suppressed by negative feedback
 - Non-suppressed (TSH) suggests → excessive TSH production by the pituitary gland → the possibility of a thyrotroph adenoma → do MRI scan pituitary gland
 - ⇒ T3 is more sensitive because occasional cases of isolated T3 toxicosis can occur.
- TSH receptor antibody (TRAb): for suspected Graves disease without characteristic features
- Thyroid ultrasound with Doppler
 - ⇒ first-line for pregnant/lactating patients, palpable nodules or suspected thyroiditis
 - ⇒ Increased perfusion: either diffuse (Graves' disease, toxic adenoma) or nodular (toxic MNG)
 - ⇒ Decreased perfusion: destructive causes of hyperthyroidism (e.g., subacute thyroiditis or postpartum destructive thyroiditis)
- Thyroid scintigraphy: Radioactive iodine uptake measurement (RAIU test)
 - ⇒ first-line for most patients with uncertain diagnoses, e.g., suspected thyroid adenoma or toxic MNG
 - ⇒ Assess functional status of thyroid nodules
 - Hot nodule: Hyperfunctioning tissue takes up large amounts of radioactive iodine
 - Cold nodule: Non-functioning nodules do not take up any radioactive iodine and appear "cold", but the surrounding normal thyroid tissue takes up radioactive iodine and appears "warm"
 - ⇒ Identify ectopic thyroid tissue
 - ⇒ Contraindications: pregnant or breastfeeding women

General laboratory findings

- ⇒ Serum glucose levels typically <u>increase</u> in patients with hyperthyroidism.
- ⇒ <u>Hypo</u>cholesterolemia due to increased LDL receptor expression.
- ⇒ Serum cholesterol: decreased total cholesterol, LDL, and HDL
- ⇒ CBC in thyrotoxic Graves' disease is most likely to show:
 - Mild leukopenia with relative lymphocytosis (mild neutropenia and lymphocytosis)
 - Normochromic anaemia
 - Rarely, thrombocytopenia.
- ⇒ High bone turnover and osteoporosis may be associated with thyrotoxicosis. Bone turnover involves increased osteoclastic and osteoblastic activity, leading to elevated alkaline phosphatase levels derived from bone.
- ⇒ Increased levels of sex hormone-binding globulin (SHBG)

Which blood tests is most sensitive in establishing whether there is excess thyroid activity?

Free T3 level

Management

- Treatment of hyperadrenergic symptoms: beta blockers (first line)
 - ⇒ Propranolol is effective in controlling all symptoms prior to initiation of specific therapy (e.g. carbimazole, which will have a more delayed effect on symptoms).
 - ⇒ If there are contraindications to beta blockers, e.g., severe asthma, Raynaud phenomenon, consider CCBs: verapamil OR diltiazem
- Antithyroid drugs (ATDs)
 - ⇒ Most patients: methimazole
 - ⇒ Thyroid storm or first trimester of pregnancy: propylthiouracil
 - ⇒ Duration of therapy for Graves' disease: typically 12–18 months
 - ⇒ Contraindications to ATDs, e.g., liver disease
- Radioactive iodine ablation (RAIA)
 - ⇒ destruction of thyroid tissue via radioactive iodine (iodine-131)
 - ⇒ Indicated for Toxic MNG, toxic adenoma and failure of antithyroid drugs (ATDs) in Graves disease.
 - ⇔ Contraindicated in pregnant/breastfeeding women and moderate to severe Graves ophthalmopathy.
- Thyroid surgery
 - ⇒ The efficacy of antithyroid drugs and RAIA has reduced the need for thyroid surgery.
 - ⇒ Indications: Large goiters (≥ 80 g) or obstructive symptoms, suspected thyroid malignancy and Graves ophthalmopathy.

Secondary thyrotoxicosis:

- Thyrotoxic with an abnormally 'normal' TSH.
- Pituitary adenoma
- Prior to pituitary surgery → restoration of euthyroidism with somatostatin analogues.

In acute thyrotoxicosis, stop aspirin as it can worsen the storm by displacing T4 from thyroid binding globulin

Thyrotoxicosis is associated with reversible cardiomyopathy

Management of thyrotoxicosis in pregnancy

Suspect a molar pregnancy or choriocarcinoma if severe hyperthyroidism manifests during pregnancy

Transient thyrotoxicosis and/or hyperemesis gravidarum

- Supportive therapy
- Management of dehydration, and hospitalization if needed.
- Anti-thyroid drugs (ATDs) are not recommended, though β-blockers may be considered.
- Early pregnancy (1st trimester) → Propylthiouracil (PTU)
 - ⇒ Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester during organogenesis and then carbimazole in trimester 2 + 3.
 - ⇒ Propylthiouracil (PTU) is highly protein bound making it less likely to cross the placenta or breast milk.
 - ⇒ Carbimazole has rarely been associated with aplasia cutis of the neonate
- Late pregnancy (2nd + 3rd trimester) → Carbimazole
 - ⇒ Propylthiouracil associated with hepatotoxicity
 - ⇒ Despite this the BNF states both drugs may be used in pregnancy.
- Postpartum Patients
 - ⇒ Carbimazole is recommended by European Thyroid Association Guideline during lactation, given the concerns about PTU-mediated hepatotoxicity.
- Contraindications
 - ⇒ Block-and-replace regimes should not be used in pregnancy
 - ⇒ Radioiodine therapy is contraindicated
- Monitoring and targets
 - ⇒ Maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism
 - ⇒ In women being treated with anti-thyroid drugs (ATDs) in pregnancy, FT4/TT4 and TSH should be **monitored approximately every 4 weeks.**
- Thyroid-stimulating hormone receptor antibodies
 - ⇒ In a patient with a past medical history of Graves' disease who is clinically and biochemically euthyroid who is planning pregnancy: check thyroid-stimulating hormone receptor antibodies (as it can cross the placenta and cause foetal problems.): If they are positive, then treatment should be initiated to control the antibody levels, despite the normal TSH and T4.

Due to the small risk of fetal abnormalities with carbimazole it is recommended to use PTU in the first trimester during organogenesis and then carbimazole in trimester 2 + 3.

A 10 weeks pregnant C/O anxiety and an inability to sleep. Blood results show: total thyroxine (T₄) 160 nmol/I (normal range 70–140 nmol/I), free T₄ 27 pmol/I (9–25 pmol/I) and thyroid-stimulating hormone (TSH) 0.2 mU/I. Which management of choice in this patient?

- · Observe and repeat thyroid function tests in one month
- Diagnosis: Physiological hyperthyroidism

Hyperthyroidism with non-suppressed TSH

- Elevated free T4 and free T3 + non-suppressed TSH (normal or elevated) = think of either:
 - ⇒ TSH-secreting pituitary tumour OR
 - **⇒** Thyroid hormone resistance
- TSH-secreting adenoma
 - ↑Alpha subunit: the next investigation to differentiate it from thyroid hormone resistance. elevated alphaSU: TSH ratio (usually 1:1). A molar ratio of Alpha subunit to TSH of > 5.7 is considered diagnostic.
 - ⇒ Pituitary MRI should be done to look for a pituitary mass.
 - ⇒ Treatment: Trans-sphenoidal resection of the tumour is the therapy of choice.
- Thyroid hormone resistance
 - ⇒ **Mechanism:** THB gene defects,
 - ⇒ **Features:** Usually <u>clinically euthyroid</u> with only goitre. Sometimes: goitre with short stature, hyperactivity, attention deficits, learning disability,
 - ⇒ **Diagnosis:** gene sequencing (sequencing the thyroid hormone receptor gene) can confirm diagnosis in 85%.
 - ⇒ Treatment: Most cases require no treatment. If needed, it is usually B-adrenergic blockers

MRCPUK-part-1-September 2007 exam: Pregnant lady investigated for excessive sweating and tremor. Blood tests reveal the following: TSH < 0.05 mu/l. T4 =188 nmol/l. What is the most appropriate management? Propylthiouracil

Toxic multinodular goitre (TNG) (Plummer's disease)

Definition

multiple autonomously functioning thyroid nodules that secrete excess thyroid hormones.

Epidemiology

- second most common cause of hyperthyroidism in the Western world, after Graves disease.
- most common cause of hyperthyroidism in <u>elderly</u> and in <u>areas of endemic iodine</u> <u>deficiency</u>.
- · Develops in 10% of patients with a long-standing nodular goiter
- Sex: ♀ > ♂
- Age: often > 60 years

Pathophysiology |

- lodine deficiency → ↓ T4 → thyroid cell hyperplasia to compensate for the low levels of T4
 → ↑thyroid cell replication → somatic mutations of the TSH receptor → further growth →
 clonal proliferation → multiple nodules.
- Somatic mutations of the TSH receptors and G α protein → activation of cyclic adenosine monophosphate (cAMP) cascade of the inositol phosphate pathways → functional autonomy of the thyroid

Features

- goiter with multiple palpable nodules
- thyrotoxicosis

 <u>Pemberton sign</u> is the <u>obstruction of the thoracic inlet</u> by extending the arms over the head, and can be positive in cases of multinodular goiter.

Diagnosis

- Ultrasonography is a highly sensitive to detect nodules
- Thyroid scintigraphy → patchy uptake
 - ⇒ Increased radioiodine uptake by multiple hyperfunctioning (hot) nodules
 - ⇒ Decreased uptake (suppression) by the rest of the gland and intervening parenchyma
- CT of the chest → is the investigation of choice to determine the degree of retrosternal involvement
- Histopathology of resected tissue: patches of enlarged follicular cells distended with colloid and with flattened epithelium

Thyroid nuclear scintigraphy

- Toxic nodular goiter (TNG) → patchy uptake.
- Graves' disease → homogeneous diffuse uptake.
- Thyroiditis → low uptake.

Treatment

- The treatment of choice is radioiodine therapy
 - ⇒ Recurrence of multinodular goitre after RAI → The next best step is a further dose
 of RAI after 6 months of the first RAI therapy.
- Surgical therapy is usually reserved for young individuals, patients with 1 or more large nodules or with obstructive symptoms, patients with dominant nonfunctioning or suspicious nodules, patients who are pregnant, patients in whom radioiodine therapy has failed, or patients who require a rapid resolution of the thyrotoxic state.

Toxic thyroid adenoma (solitary toxic nodule)

Overview

- Typically, a <u>single large thyroid nodule</u> accompanied by clinical and biochemical <u>hyperthyroidism.</u>
- This nodule is almost always benign

Pathophysiology

- Gain-of-function mutations of TSH receptor gene in a single precursor cell →
 autonomous functioning of the follicular cells of a single nodule → focal hyperplasia of
 thyroid follicular cells → toxic adenoma
- The autonomous nodule overproduces thyroid hormones → hyperthyroidism → decrease in pituitary TSH secretion → suppression of hormone production from the rest of the gland

Diagnosis

- Thyroid iodine uptake scan:
 - ⇒ Hot area surrounded by extranodular thyroid tissue.
 - ⇒ Thyroid tissue <u>surrounding</u> a toxic adenoma typically has suppressed function.
- In the absence of any thyroid auto-antibodies which argue against both Graves' disease and Hashitoxicosis, the most likely diagnosis is a solitary toxic nodule.

Treatment

- · Initial treatment
 - Control symptoms with beta-blockers and thioamides until euthyroidism is achieved, followed by tapering of beta-blockers
- Definitive treatment
 - ⇒ Non-pregnant, non-lactating adult with no mass effect:
 - 1st line → Radioactive iodine therapy
 - 2nd line → subtotal thyroidectomy
 - ⇒ Non-pregnant, non-lactating adult with mass effect:
 - 1st line → subtotal thyroidectomy
 - ⇒ Pregnant or lactating:
 - 1st line → anti-thyroid drugs
 - 2nd line → subtotal thyroidectomy

Graves' disease

Graves' disease is the most common cause of thyrotoxicosis

Overview

- Graves' disease is the most common cause of thyrotoxicosis.
- typically seen in women aged 30-50 years.
- associated with the presence of HLA-DR3 and HLA-B8
- 50% of patients with Graves disease have a family history of autoimmune disorders
- Triggers: Physical or psychological stress and pregnancy

Pathophysiology

- B and T cell-mediated autoimmunity → production of stimulating immunoglobulin G (IgG) against TSH-receptor (TRAb; type II hypersensitivity reaction) → ↑ thyroid function and growth → hyperthyroidism and diffuse goiter
- there are antibodies to the TSH receptor mimicking the action of endogenous TSH. Binding
 to the TSH receptor then activates adenyl cyclase and results in increased secretion of
 thyroid hormones (Antibodies overstimulating adenyl cyclase)

Features

- · General features of thyrotoxicosis
- · Specific features seen in Graves' but not in other causes of thyrotoxicosis
 - ⇒ Eye signs (30% of patients): exophthalmos, ophthalmoplegia
 - ⇒ Pretibial myxedema (commonly described as orange peel skin present on both shins) → pathognomonic
 - raised, indurated pinkish patches.
 - may appear years before, or after, hyperthyroidism.
 - ⇒ **Thyroid acropachy** (a dermopathy characterized by soft-tissue swelling of the hands and clubbing of the fingers). Radiographic imaging of affected extremities typically demonstrates periostitis, most commonly the metacarpal bones.
 - ⇒ Thyroid bruit: **presence of goitre is not necessary**, although usually there is a small palpable goitre.
 - ⇒ Anti-TSH receptor stimulating antibodies (90%) → specific for Graves' disease
 - ⇒ Globally increased uptake on thyroid scan.

The most likely associate of Graves' disease is vitiligo occurring in approximately 7% of cases.

Triad of Graves disease

- 1. Diffuse goiter (smooth, uniformly enlarged goiter)
- 2. Ophthalmopathy (Exophthalmos)
- 3. Dermopathy (pretibial myxedema): non-pitting edema and firm plaques on the anterior/lateral aspects of both legs

Management

- Treatment of hyperadrenergic symptoms

 → Beta blockers: first line: propranolol
- Anti-thyroid drugs (ATDs)
 - ⇒ ATD titration
 - carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
 - typically continued for 12-18 months
 - fewer side-effects than those on a block-and-replace regime
 - Long-term remission following antithyroid drugs is of the order of 15%, with the vast majority relapsing. Thus, frequently, radio-iodine is advocated as a primary treatment - particularly for multi-nodular or toxic solitary nodules.
 - ⇒ Block-and-replace
 - carbimazole is started at 40mg
 - thyroxine is added when the patient is euthyroid
 - treatment typically lasts for 6-9 months
 - this approach is associated with 50% long term remission rate (the relapse rate after treatment is 50%)
- Radioiodine iodine (RAI) treatment: in refractory cases to medical management
- Surgery: less commonly used and usually reserved for patients with <u>large goitre</u>, compressive symptoms or intolerance to antithyroid drugs and difficulties in administering radioiodine

The principal test used to follow the immediate effect of treatment of hyperthyroidism is the serum free T4 concentration. Measurement of serum TSH can be misleading in the early follow-up period because it can remain low for weeks or even months, even when the patient is biochemically euthyroid or even hypothyroid,

Which factor can be used as a <u>predictor of relapse</u> of hyperthyroidism <u>before</u> pharmacologic treatment is discontinued?

Positive thyroid-stimulating autoantibody test. (This is a good predictor of relapse, but rates of relapse are still high when thyroid-stimulating autoantibodies disappear).

Pregnant woman with a history of Grave's disease should have thyroid stimulating hormone binding antibody titres measured even if euthyroid as the antibodies can cross the placental barrier

Antithyroid drugs

Agents

- Methimazole, Carbimazole, Propylthiouracil
- Methimazole is the active metabolite of carbimazole

Mechanism of action

- Inhibits thyroid hormone production via inhibition of thyroid peroxidase → blockade of iodide oxidation, organification, coupling (Inhibition of the iodination of tyrosine)
- Propylthiouracil also lowers peripheral conversion of T4 to T3 by inhibiting 5'-deiodinase.

Onset of action

- Slow onset of action (3–4 weeks)
- Methimazole has a faster onset of action and fewer side effects than propylthiouracil

Adverse effects

- Carbimazole-induced agranulocytosis (the major complication)
 - ⇒ defined as neutrophil count less than 0.5 ×10⁹/L
 - ⇒ the incidence of leukopenia/neutropenia with carbimazole is less than 1%.
 - ⇒ should be stopped if neutrophil count below 1.5 ×10⁹/L (1.5-7).
 - ⇒ In fact, a mild decrease in WBC can also occur with hyperthyroidism.
 - ⇒ If neutrophil count are just below normal →The most appropriate treatment would be to continue the carbimazole.
 - ⇒ Treatment
 - thionamides should be withdrawn
 - appropriate antibiotics (broad spectrum cephalosporin)
 - occasionally, granulocyte colony-stimulating factor (G-CSF) is required when white count fails to respond.
- Hepatotoxicity (seen with propylthiouracil use)
- **Teratogenicity:** increased risk of congenital malformations with carbimazole and methimazole (e.g., aplasia cutis)
 - ➡ Neonatal hypothyroidism will occur in approximately 10% of babies, because carbimazole crosses the placenta and switches off the fetal thyroid axis. The goitre that occurs is transient and will disappear following delivery
 - ⇒ also, propylthiouracil cross the placenta but less freely than carbimazole , although thyroxine does not.
- Allergy/hypersensitivity
 - ⇒ pruritic rash (particularly with methimazole)
 - ⇒ ANCA-associated vasculitis (propylthiouracil)

As methimazole and carbimazole are teratogenic, propylthiouracil is recommended in the first trimester. After the first trimester, switch back to carbimazole or methimazole because of the hepatotoxic effects of propylthiouracil.

Interaction

• Carbimazole effect is potentiated by the liver enzyme-inhibitor (eg: erythromycin)

Carbimazole (CBZ) VS Propylthiouracil (PTU)

	Carbimazole (CBZ)	Propylthiouracil (PTU)	
Action	↓thyroid peroxidase	↓thyroid peroxidase + ↓5¹ deiodinase	
		type 1 \rightarrow \downarrow peripheral conversion of	
		T ₄ to T ₃	
Potency	More (15 times as potent as	Less	
	PTU)		

	Carbimazole (CBZ)	Propylthiouracil (PTU)	
Structure	less protein bound, more	more protein bound, less transfer	
	transfer across placenta	across placenta	
Teratogenicity	Associated with aplasia cutis	Less associated with aplasia cutis	
Major side effects	Agranulocytosis	Hepatotoxicity	
use in pregnancy	2 nd and 3 rd trimester	1 st trimester	

Radioactive iodine therapy (RAI)

Definition: destruction of thyroid tissue via radioactive iodine (iodine-131) **Indications**

- · Graves' disease refractory to medical management
- · Toxic multinodular goitre

Preparation before RAI

- Anti-thyroid drugs is often used prior to RAI due to the risk of early deterioration of
 thyrotoxicosis. This depletes the intrathyroidal stores of hormone to prevent reexacerbation of thyrotoxicosis in the weeks following treatment due to release of
 preformed thyroid hormone.
- Carbimazole needs to be stopped at least 7 days prior to radioiodine to ensure appropriate uptake.
- · Avoid excess iodine for 7 days prior to RAI.

Procedure

- Single oral dose of iodine-131
- The recommended dose of RAI is typically between 500 800 MBq

Advice post procedure

- Patients should be advised to keep babies, children under five, pregnant women and pets at arm's length for two to three weeks
- Females are advised to avoid pregnancy for at least 6 months after radioactive iodine treatment
- Males are advised not to cause a pregnancy for 6 months after radioactive iodine

Advantages

• Goitre shrinkage may occur in up to 30% following RAI.

Adverse effects

- Thyrotoxic symptoms
 - ⇒ Mild thyrotoxic symptoms after radioiodine occur in about one-third of patients,
 - ⇒ About 4% of patients develop a clinically significant radiation-induced thyroiditis. Should be treated symptomatically with beta blockers.
- Hypothyroidism
 - ⇒ Early post-radioiodine hypothyroidism might be transient.
 - ⇒ Hypothyroidism is the most common adverse effect.
 - ⇒ Proportion of patients who become hypothyroid
 - depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

- approximately 80% will have long-term hypothyroidism following radioiodine.
- Flare of Graves' eye disease (↑↑ thyroid eye disease in 15% of patients with Grave's disease)
 - patients with thyroid eye disease should be treated with steroids for one to two weeks prior to starting radioiodine therapy.

Contraindications

- Pregnancy
- Breastfeeding
- Active thyroid eye disease (unless providing steroid cover)
- Radioiodine therapy should be avoided until 8 weeks following CT contrast administration. the iodine in the CT contrast medium competes with the radioactive iodine (I131) for binding sites $\rightarrow \downarrow$ thyroid uptake of radioiodine.

Radioiodine therapy is the treatment of choice for patients with a relapse of Graves' disease in the absence of contraindications, such as pregnancy and active severe Graves ophthalmopathy

Thyroidectomy

Indications

- Large goiters (≥ 80 g) or obstructive symptoms
- thyroid malignancy
- Graves' disease with severe ophthalmopathy

Complications

- Transient hypoparathyroidism
 - due to local trauma at the time of surgery
 - ⇒ occur in 8 10% of cases (the most likely post-operative complication)
 - Rarely becomes permanent hypoparathyroidism in fewer than 1% of patients.
 - ⇒ Usually presents 24-48 hours postoperatively
- permanent hypoparathyroidism seen in 1-2%
- Infection is seen in 1-2%
- Bleeding is less common, seen in around 0.5% or less
- Permanent recurrent larvngeal nerve palsy occurs in 1% of patients:
 - ⇒ Recurrent laryngeal nerve injury leads to a hoarse voice, because of paralysis of the posterior cricoarytenoid muscle, which is responsible for opening the vocal cord.
 - ⇒ superior laryngeal nerve palsy affects more patients (3-4% in case series).

Which structures is most closely related to the recurrent laryngeal nerve?

- Inferior thyroid artery
- The superior thyroid artery runs closest to the superior laryngeal nerve.

Amiodarone and the thyroid gland

Overview

- Amiodarone, a class III antiarrhythmic drug can induce thyroid dysfunction (both hypo- and hyperthyroidism), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid. Amiodarone contains 75 mg of iodine per 200 mg tablet (40% iodine by weight).
- Around 1 in 6 patients taking amiodarone develop thyroid dysfunction
- Amiodarone has a wide tissue distribution, very long half-life (100 days), very lipophilic, and can result in prolonged effects even after stopping therapy for several months.

Amiodarone-induced hypothyroidism (AIH)

Epidemiology

⇒ Amiodarone-induced hypothyroidism is the commonest side effect associated with amiodarone treatment <u>in iodine replete areas</u> (in contrast to amiodarone induced thyrotoxicosis more commonly seen in iodine depleted areas).

Pathophysiology

- ⇒ High iodine content of amiodarone causing a Wolff-Chaikoff effect (an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide)
- \Rightarrow Amiodarone inhibits the peripheral conversion of T4 to T3 (normal T4 , \downarrow T3 , \uparrow TSH).

Management

- ⇒ Same as for primary hypothyroidism.
- Doses larger than normal, is often required
- Amiodarone should only be discontinued if it fails to control the underlying arrhythmia.

Amiodarone is most likely to cause a <u>false increase</u> in which of these laboratory values? Free T_4 . (Amiodarone can cause a reduced peripheral conversion of T_4 to T_3).

Amiodarone-induced thyrotoxicosis (AIT)

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

Differentiating between the two forms of Amiodarone-Induced Thyrotoxicosis (AIT)

	AIT type 1	AIT type 2
Epidemiology	Most often seen in iodine-deficient areas.	Most common in Europe and North America
Pathophysiology	Amiodarone contains↑ iodine → ↑ thyroid hormone synthesis (Jod- Basedow effect)	↑ release of T4 and T3 due to a destructive thyroiditis
history	Occurs in patients with underlying thyroid pathology, such as a nodular goitre or Graves' disease.	Occurs in patients without underlying thyroid disease.
Goitre	Present	Absent
Color Doppler	↑ Blood flow	↓ Blood flow
lodine-131 uptake scan	normal or high	Minimal or none
IL-6 levels	Low or normal	Markedly elevated
Management	Carbimazole	Corticosteroids ± Antithyroid

Differentiation between type 1 and type 2

Colour flow Doppler is most likely test to differentiate between Amiodarone induced thyrotoxicosis (AIT) type 1 and type 2. It appears to be superior to IL-6 which may be markedly elevated in AIT type 2, however may also be raised by concurrent non-thyroidal illness.

AIT initial management

- Usually Type 1 AIT is treated with high doses of anti-thyroid drugs to block thyroid hormone synthesis. Type 2 thyrotoxicosis is treated with glucocorticoids.
- Due to practical difficulties to distinguish between the 2 types, often a combination of steroids and thioamides is the best first-line management used for treatment of AIT.
 - ⇒ A rapid response suggests type 2 AIT; thionamides can be tapered.
 - ⇒ A poor initial response suggests type 1 AIT; the steroids can be tapered, and the patient can be treated for type 1 AIT.

Withdrawal of the amiodarone in AIH & AIT

- For AIH: continue amiodarone, treat with thyroid hormone. Amiodarone should only be discontinued if it fails to control the underlying arrhythmia.
- For type I AIT:
 - ⇒ Amiodarone should not be discontinued until hyperthyroid symptoms are well controlled with thionamides, since worsening hyperthyroid symptoms due to increased T3 levels may occur when the amiodarone is discontinued.
- For type 2 AIT:
 - Amiodarone should be stopped, if possible (if the patient does not have a lifethreatening arrhythmia that requires amiodarone therapy. In cases such as VT, this decision should be considered carefully in conjunction with a cardiologist, so the next management step will be Start carbimazole 40 mg od.
 - ⇒ **Discontinuation of the drug has no immediate benefit.** Even if amiodarone is stopped, thyrotoxicosis persists for up to 8 months because of the drug's long half-life.

The presence of markedly **elevated serum IL-6** and low thyroidal radioiodine uptake in a patients without underlying thyroid disease suggests the presence of **amiodarone-induced thyroiditis** as the etiology of thyrotoxicosis.

Thyroid eye disease

Feature	Assessment	Frequency
Lid lag / lid retracted	Measure lid fissure width	50-60%
Grittiness, discomfort, periorbital oedema, pain, excessive tears.	Self-assessment score by patient	40%
Proptosis (aka exophthalmos) this is where the eye bulges out of its socket.	Exophthalmometry or evaluation on MR/CT scan.	20%
Extraocular muscle dysfunction –typically causes diplopia (double vision) when looking up and out.	Hess chart + CT/MR to detect muscle size	10%
Corneal involvement, causing exposure keratitis	Flourescin staining	<5%
Loss of sight due to optic nerve compression	Visual acuity tests, visual field tests. CT/MR scan	<1%

Overview

- Also called Graves' Ophthalmopathy or Graves' eye disease
- Graves' eye disease can occur in euthyroid, hypothyroid or hyperthyroid setting.
- Thyroid eye disease affects between 25-50% of patients with Graves' disease.
- In about 10% of patients, the signs will only be unilateral.
- Ophthalmopathy may occur before the onset of hyperthyroidism, or as late as 20 years afterward.
- **Risk factors** for the development of Graves' orbitopathy include genetics, female sex, smoking, and prior radioiodine therapy.

Graves' eye disease can occur in euthyroid, hypothyroid or hyperthyroid setting.

Definitions

- Exophthalmos (also known as proptosis) is the protrusion of one eye or both anteriorly
 out of the orbit.
- Lid retraction: When looking at the patient from the side, you see that the eyes are proptosed.
- Lid lag: When the patient follows your finger, moving downwards from above, the sclera can temporarily be seen above the iris.

Pathophysiology

- TSH autoantibodies are present in the orbital cavity; bind TSH receptor antigen
 (autoimmune reaction) on cells; lymphocytic infiltration into the orbital tissues →
 inflammation and release of cytokines from CD4+ T cells → stimulates fibroblasts to secrete
 glycosaminoglycans (hyaluronic acid); expansion of retro-orbital tissue → infiltrative
 ophthalmopathy (exophthalmos). the most likely underlying pathogenesis →
 Excessive fibroblast proliferation
- in case of reduced vision with colour desaturation, the most likely mechanism is \to Optic nerve $\underline{\text{compression}}$
- Hyperthyroidism → stimulates the beta receptors of the third cranial nerve → stimulates the levator palpebrae superioris muscle → Pull up the evelid → lid lag and lid retraction

Which eye signs are specific to Graves' disease?

Eye signs specific to Graves' disease	Eye signs found in most thyrotoxic states	
 Proptosis 	Both lid lag and lid retraction reflect enhanced	
 Ophthalmoplegia 	sensitivity to circulating catecholamines and may	
Chemosis	therefore be found in most thyrotoxic states.	
Periorbital oedema		

Prevention

- Avoid smoking
- Patients with thyroid eye disease are generally treated with steroids for one to two
 weeks prior to starting radioiodine therapy. Radioiodine treatment →↑↑ thyroid eye
 disease → malignant exophthalmos. Prednisolone may help reduce the risk.
- In patients with thyroid eye disease undergoing radioiodine treatment, post-radioiodine
 hypothyroidism should be avoided, because of the risk of worsening Grave's eye
 disease. For this reason, patients are stabilised on a block replace regimen before
 moving to radioiodine therapy.

Smoking is the most important modifiable risk factor for the development of thyroid eye disease

Investigations

- Thyroid function tests: ↓ TSH and ↑ free T3/T4; ↑ TSH receptor antibodies
- Noncontrast CT scan of the orbits: the initial image of choice
 - ⇒ assess the risk of future optic nerve compression by enlarged extraocular muscle at the orbital apex.
 - ⇒ measure the of proptosis and retroocular fat accumulation
 - ⇒ helpful in the differential diagnosis
- MRI of her orbits: certainly demonstrate retro-orbital and extraocular muscle inflammation.

Management

- Eye protection: local measures (e.g. artificial tears (saline eye drops), raising the head of the bed at night), topical lubricants to prevent corneal inflammation caused by exposure
- Mild orbitopathy: local measures are usually effective to relieve eye symptoms, and no additional treatment is needed.
- Moderate-to-severe orbitopathy → glucocorticoids is the initial therapy.
- Avoid smoking
- Treat hyperthyroidism (if present): by thionamides, radioiodine, or surgery.
 - ⇒ Radioactive iodine ablation (RAIA) can be used for patients with active **mild** disease. **Moderate-to-severe** is a contraindication to radioiodine therapy.
 - ⇒ Although radioiodine could exacerbate Graves' ophthalmopathy, radioiodine treatment can safely be given to patients with inactive Graves' ophthalmopathy with steroid cover, provided hypothyroidism is avoided.
- For sight-threatening (malignant exophthalmos, diplopia and loss of colour vision)
 - ⇒ The initial treatment is IV glucocorticoids (dexamethasone, 4 mg IV)
 - ⇒ Surgical orbital decompression may be necessary: performed 1-2 weeks after IV glucocorticoids if the response is poor.

Indications of urgent review by an ophthalmologist

- · Unexplained deterioration in vision
- · Awareness of change in intensity or quality of colour vision in one or both eyes
 - ⇒ Impaired perception of colour implies → acute progressive neuropathy.
- History of eye suddenly 'popping out' (globe subluxation)
- · Obvious corneal opacity
- · Cornea still visible when the eyelids are closed
- Disc swelling

If there is active Grave's eye disease, then radioiodine therapy is not recommended as it can worsen the eye disease

Thyroid storm (crisis)

In a patient with thyroid storm with high heart rate over 170bpm and low blood pressure the most urgent management is IV beta-blocker

Thyrotoxic storm is treated with beta blockers, propylthiouracil and hydrocortisone

Overview

- An acute exacerbation of hyperthyroidism that results in a life-threatening hypermetabolic state.
- Thyroid storm is a rare but life-threatening acute exacerbation of thyrotoxicosis.
- Associated with a significant mortality rate (30-50%)
- It is typically seen in patients with established thyrotoxicosis and is rarely seen as the
 presenting feature.
- latrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating factors

- Any acute stressful condition such as surgery or trauma
- Acute infections
- Acute iodine load e.g. CT contrast media
- Postpartum
- When antithyroid drugs are being withdrawn.

Clinical features include

- Altered mental status (confusion, agitation)
- Fever > 38.5C
- Tachycardia
- Nausea, vomiting, and diarrhea
- Jaundice
- Hypertension
- Multisystem decompensation: heart failure, respiratory distress, prerenal failure, abnormal liver function test.

Diagnosis

Low/undetectable TSH, elevated free T3/T4 (but may not be grossly elevated)

Management

- Transfer the patient to the Intensive Care Unit
- Symptomatic treatment
 - ⇒ Tachycardia: beta blockers, first-line → propranolol
 - ⇒ Hypotension and hypovolemia: fluid resuscitation
 - ⇒ Hyperpyrexia → Paracetamol
 - ⇒ Agitation → chlorpromazine (also can be useful in treating the hyperpyrexia because of its effect in inhibiting central thermoregulation)
- · Antithyroid drugs in thyroid storm
 - ⇒ Inhibition of thyroid hormone synthesis: First line → propylthiouracil
 - ⇒ Inhibition of thyroid hormone release (through the Wolff-Chaikoff effect): First line → Potassium iodide solution given at least 1 hour after antithyroid drugs
 - ⇒ Inhibition of peripheral conversion of T4 to T3: Glucocorticoids → First line: hydrocortisone, alternative: dexamethasone
 - ⇒ Inhibition of enterohepatic circulation of thyroid hormones: bile acid sequestrants → cholestyramine
 - ⇒ Plasmapheresis and peritoneal dialysis may be effective in cases resistant to the usual pharmacological measures.

In thyroid storm, treat acutely with propylthiouracil rather than carbimazole

lodine in CT contrast media can precipitate thyrotoxicosis or thyroid storm

Treatment of thyroid storm, five 'Bs':

- 1. Block synthesis (i.e. antithyroid drugs);
- 2. Block release (i.e. iodine):
- 3. Block T4 into T3 conversion (i.e. high-dose propylthiouracil, propranolol, corticosteroid);
- 4. Beta-blocker.
- 5. Block enterohepatic circulation (i.e. cholestyramine).

Thyroid cancer

Epidemiology

- · accounts for <1% of all cancer
- commonest in adults aged 40–50
- ♀ are affected more than ♂.

Causes

- · Genetic factors
 - ⇒ Medullary carcinoma: associated with MEN2 (RET gene mutations)
 - ⇒ Papillary carcinoma: associated with RET/PTC rearrangements and BRAF mutations
 - Follicular carcinoma: associated with PAX8-PPAR-γ rearrangement and RAS mutation
 - ⇒ Undifferentiated/anaplastic carcinoma: associated with TP53 mutation
- **lonizing radiation**; associated with papillary carcinoma

Classification

• There are five main types of thyroid carcinoma and their properties are given below:

Cell type	Frequency	Behaviour	Spread	Prognosis
Papillary	80%	Often young females present as "cold nodules" on isotope scanning	Local – Lymph node mets predominate	excellent
Follicular	10%	More common in females	Haematogenous	Good
Medullary cell	5%	Often familial. Cancer of parafollicular cells (c cell), secrete calcitonin, part of MEN-2	Local and mets	Poor
lymphoma	2%	*almost always non-Hodgkin lymphomas * Associated with Hashimoto's *often elderly women.	Locally invasive	Poor
Anaplastic	~ 1–2%	Aggressive, Not responsive to treatment, can cause pressure symptoms	Haematogenous	Very Poor

Papillary carcinoma is the most Prevalent type of thyroid cancer, it features Palpable lymph nodes, and it has the best Prognosis compared to all other types of thyroid cancer.

Medullary thyroid carcinoma (MTC)

- C cells derived from neural crest and not thyroid tissue
- Systemic effects of calcitonin → flushing/diarrhoea
- The best screening and diagnostic test: pentagastrin stimulation test. It measures calcitonin levels at 2 and 5 minutes after pentagastrin infusion, and a rise in calcitonin is suggestive of medullary thyroid carcinoma.
- Investigations to exclude MEN 2 should be done:
 - ⇒ serum calcium to exclude hyperparathyroidism
 - □ metanephrines to exclude phaeochromocytoma. Exclusion of
 phaeochromocytoma is crucial before thyroidectomy → abdominal MRI,
 because any major surgery can precipitate hypertensive crisis due to release of
 massive amounts of catecholamines.
 - ⇒ genetic testing for RET mutation
- Need geniting screening. Germline RET mutation carriers should undergo thyroidectomy before 5 years of age.

Thyroid lymphoma

- Associated with preexisting chronic autoimmune (Hashimoto's) thyroiditis
- The best choice of therapy is combined chemotherapy with local radiation therapy.

Features

- May be asymptomatic
- Thyroid nodule: Firm to hard, Typically painless
- Features of local infiltration or compression: recent onset of: hoarseness of voice, dyspnea or dysphagia

Diagnosis

- Thyroid ultrasound:
 - ⇒ the initial investigation of choice in small non-symptomatic thyroid mass
 - ⇒ sonographic signs of thyroid cancer
 - Solid or mostly solid hypoechoic nodule(s)
 - Irregular margins
 - Microcalcifications
 - taller than wide
- Fine-needle aspiration cytology (FNAC): Confirmatory test
 - ⇒ The appropriate investigation after ultrasound
- Thyroid scintigraphy → decreased or no radiotracer uptake (i.e., hypofunctioning or nonfunctioning nodules, referred to as cold nodules)
- Thyroid cancer tumor markers
 - ⇒ **Follicular or papillary thyroid cancer:** Thyroglobulin (Tg): precursor of thyroid hormones; produced exclusively by the thyroid gland. Indicated after total thyroidectomy or RAIA therapy
 - ⇒ **Medullary carcinoma:** Calcitonin: A hormone secreted by parafollicular cells, which is the tissue of origin of medullary carcinoma
 - supportive diagnostic marker
 - monitor response to therapy

Medullary thyroid cancer - calcitonin is used for screening, prognosis and monitoring

Follicular thyroid carcinoma VS follicular adenoma.

- Fine-needle aspiration (FNA) biopsy alone cannot distinguish
- The actual diagnosis of follicular thyroid cancer requires histologic evaluation of the thyroid after surgery and the identification of tumor capsule and/or vascular invasion.
- Follicular carcinoma invades the thyroid capsule and vasculature, unlike a follicular adenoma.

Pathology

- Papillary thyroid carcinomas:
 - ⇒ **Psammoma bodies** (concentric lamellar calcifications)
 - ⇒ "Orphan Annie" eyes nuclei (empty-appearing large oval nuclei with central clearing)
 - ⇒ Nuclear grooves
- Follicular carcinoma
 - ⇒ Uniform follicles
 - ⇒ Vascular and/or capsular invasion
- Medullary carcinoma
 - ⇒ Ovoid cells of C cell origin and therefore without follicle development
 - ⇒ Amyloid in the stroma (stains with Congo red)
- Anaplastic thyroid carcinoma
 - ⇒ Undifferentiated giant cell (i.e., osteoclast-like cell)

"Papi and Moma adopted Orphan Annie:" papillary thyroid cancer is histologically characterized by psammoma bodies and Orphan Annie-eye nuclei.

Medullary carcinoma is composed of C-cells producing Calcitonin and is characterized by amyloid aCCumulation staining with Congo red.

Which proto-oncogenes is most associated with papillary carcinoma of the thyroid?

- Trk is a proto-oncogene, mutation of which leads to activation of tyrosine kinase receptors.
- Trk activation is thought to play a role in the pathogenesis of papillary thyroid carcinoma

Management: Surgical resection is the primary treatment for thyroid cancer.

- Total thyroidectomy +/- neck dissection as needed (e.g., in patients with regional lymph node spread)
- · Hemithyroidectomy: Indications
 - ⇒ Small, well-differentiated thyroid carcinoma with all of the following characteristics:
 - Intrathyroidal tumors (i.e., no evidence of extrathyroidal extension)
 - No nodal or distant metastasis
 - No high-risk patient factors
 - ⇒ Preferred option in tumors < 1 cm in size
 - ⇒ An alternative to total thyroidectomy in tumors 1–4 cm in size
 - ⇒ Contraindications
 - Intrathyroidal tumor ≥ 4 cm
 - Extrathyroidal spread
 - Distant or nodal metastasis

Adjuvant therapy

- ⇒ Well-differentiated thyroid cancer
 - Radioactive iodine ablation (RAIA): conducted 4– 6 weeks after total thyroidectomy to destroy remaining thyroid tissue or metastases
 - TSH suppression therapy: → thyroxine after completion of RAIA
- ⇒ Poorly differentiated thyroid cancer: adjuvant radiation therapy and/or chemotherapy
- Post-operative thyroid replacement therapy (thyroxine)
 - ⇒ The aim: titrate the thyroxine dose to **suppressed TSH levels**:
 - in high risk thyroid cancers: TSH levels should be less than 0.1 mU/L
 - In intermediate risk cancers: TSH can be maintained between 0.1- 0.5
 - In low risk thyroid cancer target **TSH** to be in **0.5-2.0** range.
 - ⇒ Most patients will require 175 or 200 µg daily.

• Post-operative follow-up

- ⇒ yearly thyroglobulin (Tg) levels to detect early recurrent disease (thyroid is the only source of thyroglobulin).
- ⇒ The most appropriate investigation at annual follow-up for papillary thyroid cancer.
 - Ultrasound scan is the most sensitive investigation for the detection of locally recurrent papillary carcinoma.
 - Other investigations should be considered if ultrasound scan is negative or distant metastases are suspected. (SCE. Questions sample. Mrcpuk.org).

Thyroid cancer treatment \rightarrow Thyroidectomy and neck dissection with postoperative radioiodine ablation

Thyroid cancer associated with Graves' disease is not uncommon and usually due to papillary carcinoma and must be considered in suspicious/expanding nodules rather than attributing purely to Graves' disease.

 hyperthyroidism with prominent nodule which is 'cold' on uptake scanning is highly suggestive of thyroid carcinoma and the mostly likely diagnosis is Graves' disease (periorbital puffiness and thyroid bruit) associated with papillary thyroid carcinoma.

The association of Horner's syndrome and a thyroid nodule suggest invasion of the sympathetic chain and suggest that this thyroid nodule is malignant.

Which familial condition carries an increased risk of papillary carcinoma of the thyroid?

 Gardner's syndrome (intestinal tumours & lipomas. Also Osteomas & fibromas). carries an increased risk of papillary carcinoma

Which test is most useful in the assessment of airflow obstruction due to the retrosternal goitre?

Flow volume curve

Thyroid nodule and fine-needle aspiration

Epidemiology

 About 50% of the general population have single or multiple thyroid nodules, whereas the incidence of thyroid malignancy is 2–4%.

Thyroid ultrasound

- Ultrasonographic criteria associated with higher risk of malignancy:
 - 1) Low echodensity (Hypoechogenicity)
 - 2) Microcalcifications: the most predictive feature of malignancy
 - 3) Irregular borders (poorly-defined margin)
 - Increased <u>intranodular</u> vascularity: (↑↑marginal blood flow → benign adenoma, ↑↑ <u>intranodular</u> blood flow → thyroid cancer)
 - 5) Absence of a halo
 - 6) Taller-than-wide configuration on transverse view
- Referral of a thyroid nodule: (British Thyroid Association (BTA) guidelines)

Same day	Urgent	Non-Urgent	Managed by GP
Stridor associated with thyroid lump	Palpable cervical lymph nodes	Patient with hyper or hypothyroidism refer to endocrinologist	No change in size over years
	Rapidly enlarging (days-weeks)	Lump enlarging over months	No known risk factors
	Presence of risk factors for thyroid cancer	Sudden pain and enlarged mass (bleeding in a cyst)	<1cm, incidental thyroid nodule
	Hoarseness of voice		
	Nodule in a child		

• Ultrasound "U" classification of thyroid nodules

Classification	Criteria
U1 (normal)	- no nodules
U2 (benign)	- hyperechoic or isoechoic with a halo
	- cystic change with ring down artiifact (colloid)
	- microcystic or spongiform appearance
	- peripheral egg-shell calcification
	- peripheral vascularity
U3	- solid homogenous markedly hyperechoic nodule with halo (follicular
(indeterminate)	lesions)
	- hypoechoic with equivocal echogenic foci or cystic change
	- mixed or central vascularity
U4 (suspicious)	- solid hypoechoic (compared with thyroid)
	- solid very hypoechoic (compared with strap muscles)
	- hypoechoic with disrupted peripheral calcification
	- lobulated outline
U5 (malignant)	- solid hypoechoic with a lobulated or irregular outline and
	microcalcification (papillary carcinoma)
	- solid hypoechoic with a lobulated or irregular outline and globular
	calcification (medullary carcinoma)
	- intranodular vascularity
	- taller than wide axially (AP>ML)
	- characteristic associated lymphadenopathy

• The need for Fine Needle Aspiration Cytology (FNAC) according to US:

	The need for time research replication sylving (1 three) describing to ser			
	U1-2	not requiring FNAC, unless the patient has a statistically high risk of malignancy		
I	U 3 - 5	FNAC should be done		

Fine needle aspiration (FNA)

 the gold standard diagnostic tool for thyroid nodules. but follicular neoplasia can only be diagnosed histologically. Diagnostic categories from FNAC (The royal college of pathologist classification)

	Category	Action
Thy 1	Non-diagnostic. Inadequate	Repeat sampling, using US if necessary
Thy 2	Non-neoplastic	Two samples, 3–6 months apart, showing benign appearances are indicated to exclude neoplasia. If rapid growth/pressure effects/high risk, diagnostic lobectomy may be indicated
Thy 3 (Thy3f)	(i) Follicular lesions	Lobectomy (diagnostic hemithyroidectomy) (because follicular adenoma or follicular carcinoma cannot be distinguished on cytology alone) with completion thyroidectomy if malignant (up to 20% risk of malignancy)
Thy 3 (Thy3a)	(ii) a typical features, other suspicious findings	Many Thy3a cases reflect suboptimal specimens → Discussion at thyroid cancer MDT → Repeat FNAC
Thy 4	Suspicious of malignancy	Surgical excision for differentiated tumour (80% risk of malignancy) (diagnostic hemithyroidectomy)
Thy 5	Diagnosis of malignancy	Surgical excision for differentiated thyroid cancer (>95% risk of malignancy). Radiotherapy/ chemotherapy for anaplastic thyroid cancer, lymphoma/metastases

Calcium metabolism

Overview

- The average adult store of calcium is approximately 1–2 kg.
- Recommended daily dietary calcium requirement: 1 1.5 g per day.
- Bones are the major storage site of calcium (99%)
- Plasma Ca2+ exists in three forms:
 - Ionized/ free (~45%,active form): The most important form in regulation of body functions
 - **2.** Bound to albumin (\sim 40%)
 - **3.** Bound to anions (\sim 15%)

Actions of the Hormones Involved in Calcium Homeostasis

HORMONE	EFFECT ON BONES	EFFECT ON GUT	EFFECT ON KIDNEYS
Parathyroid hormone →↑Ca ⁺⁺ , ↓PO ₄ levels in blood	↑osteoclastic activity	Indirect effects via †calcitriol from 1- hydroxylation	↑Ca ⁺⁺ resorption and PO ₄ excretion, activates 1-hydroxylation → ↑ conversion of 25- hydroxycholecalciferol to 1,25- dihydroxycholecalciferol
Calcitriol (vitamin D) ↑Ca ⁺⁺ ,↑PO ₄ levels in blood	↑osteoclastic activity	↑Ca ⁺⁺ and PO ₄ absorption	↑renal tubular reabsorption of Ca ⁺⁺ and PO ₄
Calcitonin causes ↓Ca ⁺⁺ , ↓PO ₄ levels in blood when hypercalcemia is present	Inhibits osteoclast resorption	No direct effects	Promotes Ca ⁺⁺ and PO ₄ excretion

Effects of pH and albumin changes on Ca2+ homeostasis

- Ca2+ competes with H+ to bind to albumin
- ↑ pH (less H+) → albumin binds more Ca2+ → ↓ionized Ca2+ (eg, cramps, pain, paresthesias, carpopedal spasm) → ↑ PTH
- \downarrow pH (more H+) \rightarrow albumin binds less Ca2+ \rightarrow \uparrow ionized Ca2+ \rightarrow \downarrow PTH
- Even if the total extracellular fluid (ECF) calcium stays constant, the bound percentage can
 vary, increasing with alkalosis and decreasing with acidosis. So if the free concentration
 percentage falls, hypocalcemia symptoms may occur even though the total measured ECF
 calcium has not changed.
- Hypoproteinemia (due to, e.g., nephrotic syndrome, liver cirrhosis, severe malnutrition, malabsorption) → ↓ total Ca2+ level but ionized Ca2+ level is unaffected; → factitious hypocalcemia (*Pseudohypocalcemia*)

To remember the effect pH has on PTH, think: \uparrow pH = \uparrow PTH and \downarrow pH = \downarrow PTH.

Absorption

- intestinal absorption of calcium is facilitated by →1,25 dihydroxy-vitamin D, which stimulates the microvillous membrane of the enterocyte to synthesise the calcium-binding carrier protein necessary for active calcium ion absorption.
- 99% of filtered calcium is reabsorbed in the kidneys, around 55% in the proximal convoluted tubule

Excretion

- Calcitonin is the most important factor regulating calcium excretion.
- <u>Calcitonin</u> is secreted by the parafollicular cells of the thyroid gland and responds to raised calcium levels by inhibiting bone resorption and increasing renal excretion
- calcium excretion is heavily influenced by sodium excretion. <u>Low-sodium diets tend to</u> decrease Ca excretion and vice versa.
- The concentration of calcium in urine reflects serum calcium.

All patients should maintain a **daily total calcium intake** (diet plus supplement) of **1000 mg** (for ages 19 to 70 years) to **1200 mg** (for women ages 51 through 70 years and all adults 71 years and older)

Hypercalcaemia

hyperparathyroidism → ↑Ca⁺⁺, ↓PO₄ levels

90% of hypercalcemia are caused by primary hyperparathyroidism and

Thiazides cause hypercalcaemia, might unmask underlying primary hyperparathyroidism (PHPT), as they cause mild hypercalcemia by reducing urinary calcium excretion.

Definition

· Corrected calcium of more than 2.6 mmol/l.

Causes

- Primary hyperparathyroidism (normal or ↑ PTH, ↑ serum Ca⁺⁺, ↓PO₄): the commonest cause
- Malignancy
 - ⇒ Hypercalcaemia occurs in 20% to 30% of patients with cancer.
 - ➡ Most common cause: paraneoplastic production of PTHrP (e.g., squamous cell carcinomas of the lung, head, and neck; breast, ovarian, bladder, and renal cancer; lymphoma and leukemia)
 - ⇒ Osteolytic metastases (e.g., multiple myeloma, breast cancer, lymphoma and leukemia, renal cancer) → Skeletal survey is the best initial investigation to contribute to the underlying diagnosis
 - ⇒ Paraneoplastic production of 1,25-dihydroxyvitamin D: e.g., lymphoma.
 - ⇒ <u>suppressed PTH</u>, hypercalcaemia without hypophosphataemia. phosphate will be low in PTHrP-mediated hypercalcaemia.
- Familial hypocalciuric hypercalcaemia: autosomal dominant mutations in the calcium sensing receptor gene, leading to calcium hyposensitivity (↑ serum Ca⁺⁺, ↑ or normal PTH, ↓urine Ca⁺⁺).
- Vitamin D intoxication: due to ↑ supplementation, ↑sun exposure →↑ vitamin D production → ↑vitamin D (1,25 OH cholecalciferol), ↑ serum Ca⁺⁺, normal or ↓ PTH)
- Drug induced
 - ⇒ Thiazides → ↓ excretion → hypercalcaemia (but furosemide → hypocalcaemia)
 - ⇒ calcium containing antacids
 - ⇒ **lithium** → ↑ release of PTH
 - ⇒ Vitamin A toxicity (including analogs used to treat acne)
 - ⇒ Theophylline toxicity
- Tertiary hyperparathyroidism: Usually seen in patients with ESRD
 - ⇒ Renal failure → chronic secondary hyperparathyroidism → autonomous (unregulated) activation of one or more parathyroid gland. (Note that secondary hyperparathyroidism is a response to hypocalcaemia, not a cause of hypercalcaemia).
- Hyperthyroidism: ↑ serum Ca⁺⁺, normal or ↓ PTH, ↓ TSH
- Milk-alkali syndrome: ↑ serum Ca⁺⁺, normal or ↓ PTH
 - ⇒ Cased by consumption of large amounts of calcium carbonate
 - ⇒ Presents with a triad of hypercalcemia, metabolic alkalosis (↑bicarbonate), and acute kidney injury
- Sarcoidosis → activated pulmonary macrophages → ↑vitamin D → ↑intestinal absorption of Ca → ↑Ca
- Prolonged immobilisation: ↑ serum Ca⁺⁺, nondetectable PTH
 - ⇒ Lack of weight-bearing activities → osteoclast activation → bone demineralization → hypercalcemia
- Paget's disease: ↑ serum Ca⁺⁺, nondetectable PTH
- Williams' syndrome: a rare genetic disease affecting chromosome 7 and characterised by hypercalcaemia, unusual "elfin" appearance, with a low nasal bridge, anxiety and learning disability.
- Acromegaly
- Dehydration
- · Addison's disease
- Infections: HIV, histoplasmosis

Differentiate between hypercalcaemia in primary hyperparathyroidism and malignancy:

- · in primary hyperparathyroidism
 - ⇒ Parathyroid hormone is elevated or normal
 - ⇒ calcium level is often < 3 mmol/l
 - Hypercalcaemia is often asymptomatic and might have been present for months or vears.
 - ⇒ Chronic symptoms are more consistent with hyperparathyroidism, whereas more recent onset of symptoms suggests malignancy.
- in malignancy
 - ⇒ patients are usually acutely ill
 - ⇒ often with neurological symptoms
 - ⇒ calcium level is usually > 3 mmol/l
 - ⇒ Parathyroid hormone is suppressed
 - ⇒ Cancer (eg lung, breast or myeloma) is often clinically apparent.

Features

- Bones: Bone pain, malaise, fatigue, muscle weakness
- Stones: Nephrolithiasis
- Groans: abdominal pain, constipation, peptic ulcer disease, pancreatitis
- Thrones: polydipsia and polyuria
- Pyschic moans: impaired concentration, confusion, hyporeflexia, depression
- Cardiovascular manifestations: short QT interval → ↑ risk of cardiac arrhythmias.

Mechanism of volume depletion in hypercalcaemia

- ↑calcium → ↓effect of ADH on the collecting duct → nephrogenic diabetes insipidus.
- ↑calcium → osmotic diuresis.

The presentation of hypercalcemia includes stones (nephrolithiasis), bones (bone pain, arthralgias), thrones (increased urinary frequency), groans (abdominal pain, nausea, vomiting), and psychiatric overtones (anxiety, depression, fatigue).

Hypercalcemia can cause pancreatitis. Hypocalcemia in patients with pancreatitis suggests pancreatic necrosis.

Management

- Supportive care
 - ⇒ Hydration
 - ⇒ Identify and treat the underlying cause
 - ⇒ Reduce dietary intake of calcium
 - ⇒ Avoid; thiazides; lithium
- Severe hypercalcemia (Ca⁺⁺ >3.5 mmol/L) and symptomatic moderate hypercalcemia (Ca⁺⁺ 3.0–3.5 mmol/L):
 - ⇒ Start IV fluid therapy with 0.9% NaCl. the initial management of hypercalcaemia
 - ⇒ **Loop diuretics in association with saline infusion** to increase calcium excretion.
 - It may be useful in patients who cannot tolerate aggressive fluid rehydration (e.g. heart failure and renal impairment) or if more rapid lowering of serum calcium is desired.
 - \Rightarrow **Bisphosphonates** (I.V) to inhibit osteoclast activity $\rightarrow \downarrow$ bone turnover.
 - The most appropriate next step after hydration
 - take 2-3 days to work with maximal effect being seen at 7 days

- Options include pamidronate disodium and zoledronic acid, which are both administered as a single dose.
- ⇒ **Calcitonin** to inhibit osteoclast activity and enhance urinary excretion of calcium.
 - quicker effect than bisphosphonates
 - Refractory hypercalcaemia of malignancy may be treated with subcutaneous calcitonin if therapy with fluids and pamidronate fails
 - calcitonin use is limited by its transient effect, association with anaphylaxis and availability.
- ⇒ Steroids in sarcoidosis
- ⇒ Consider haemodialysis for refractory life-threatening hypercalcemia or if other therapies are contraindicated

Thiazide diuretics enhance Tubular calcium upTake: Discontinue them in hypercalcemia. Loop diuretics Lose calcium: They may be used to treat fluid overload in patients with hypercalcemia.

Familial hypocalciuric hypercalcaemia (FHH)

Pathophysiology

 autosomal dominant inactivating mutation in the CaSR gene → decreased sensitivity of G-coupled calcium-sensing receptors in parathyroid glands and kidneys; higher reabsorption of Ca2+ in the kidney → hypocalciuria with mild hypercalcemia and normal or increased PTH levels

Features

- Usually asymptomatic (often diagnosed incidentally)
- Neonatal hypocalcemia in children of mothers with FHH (e.g., paresthesias, muscle spasms, seizures)

Diagnosis

- Hypercalcemia and inappropriately normal or increased PTH
- Hypocalciuria
- a two-step diagnostic procedure is recommend (The diagnostic sensitivity of this setup is 98%)
 - ⇒ First, the calcium/creatinine clearance ratio is measured from a 24-h urine.
 - ⇒ Second, all patients with calcium/creatinine clearance ratio of 0.020 or less are tested for mutations in the CASR gene (Request calcium sensing receptor mutational analysis)
- No evidence of end organ damage (normal renal function, absence of nephrolithiasis, no evidence of bone disease)

Treatment

No treatment necessary

Hypocalcaemia

Causes

- Vitamin D deficiency (osteomalacia) (Osteomalacia causes hypocalcaemia associated with a low serum phosphate)
- · Chronic renal failure
- Hypoparathyroidism (e.g. post thyroid/parathyroid surgery)

- Pseudohypoparathyroidism (target cells insensitive to PTH) (short fourth finger, round face, and mental retardation)
- Rhabdomyolysis (initial stages)
- Magnesium deficiency: (Magnesium is needed to release PTH from the gland)
 - ⇒ Hypomagnesemia → ↓ PTH secretion or induces PTH resistance → hypocalcemia
 - ⇒ Causes:
 - ileostomies → magnesium loss through stomas → hypomagnesaemia
 → ↓ PTH → hypocalcaemia that is resistant to an increased provision of calcium
 - end organ PTH resistance
 - Long term alcoholism → significant falls in magnesium → persistently decreased calcium despite replacement
 - Omeprazole and PPI → ↑GI magnesium losses → hypomagnesaemia → impairs the calcium sensing on the parathyroid cells → hypoparathyroidism →hypocalcaemia.
- Hyperphosphatemia: Phosphate binds with the calcium and lowers it.
 - ⇒ ↓ Renal excretion of phosphate (e.g., impaired renal function)
 - ⇒ Increased phosphate intake (e.g., oral supplements, enemas)
 - ⇒ Increased tissue breakdown (e.g., tumor lysis syndrome, rhabdomyolysis, crush injury)
- Fat malabsorption: This binds calcium in the gut.
- Massive blood transfusion
 - \Rightarrow anticoagulant **citrate** in the bags \rightarrow **citrate accumulation** in blood \rightarrow chelates (binds to) circulating ionized calcium (iCa) \rightarrow _plasma iCa.
- · Acute pancreatitis may also cause hypocalcaemia.
- Contamination of blood samples with EDTA may also give falsely low calcium levels
- Pseudohypocalcemia: Due to gadolinium contrast agent or hypoalbuminemia
- Hyperventilation: Redistribution of calcium
- Drug induced: e.g: Loop diuretics increase renal calcium excretion.

Hypocalcemia is most often due to hypoparathyroidism or vitamin D deficiency (e.g., malabsorption, chronic kidney disease).

Magnesium deficiency causes hypocalcaemia

- ↓↓ calcium and phosphate + ↑↑alkaline phosphatase → Osteomalacia
- normal calcium and phosphate + ↑↑alkaline phosphatase → Paget's disease
- Serum biochemistry is normal in osteoporosis, although alkaline phosphatase can be elevated following a fracture.

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen as a result of neuromuscular excitability

Features

- Tetany: increased neuromuscular excitability (when caused by respiratory alkalosis = hyperventilation-induced tetany): muscle twitching, cramping and spasm
 - ⇒ Paresthesias: typically tingling or pins-and-needles sensation in extremities and/or in the perioral area
 - ⇒ **carpopedal spasm** (wrist flexion and fingers drawn together)
 - ⇒ Bronchospasm, larvngospasm

- Seizure
- If chronic: depression, cataracts
- Maneuvers to elicit latent tetany on physical exam
 - Trousseau sign: ipsilateral carpopedal spasm occurring several minutes after inflation of a blood pressure cuff. seen in around 95% of patients with hypocalcaemia and around 1% of normo-calcaemic people
 - Chvostek sign: short contractions (twitching) of the facial muscles elicited by tapping the facial nerve below and in front of the ear. seen in around 70% of patients with hypocalcaemia and around 10% of normo-calcaemic people
- Hyperreflexia
- ECG changes
 - ⇒ Common: Corrected QT interval prolongation
 - ⇒ Rare: Atrial fibrillation or torsade de pointes

Parathyroid hormone is the single most useful test in determining the cause of hypocalcaemia

Hypocalcaemia: Trousseau's sign is more sensitive and specific than Chvostek's sign

Signs of neuromuscular irritability (e.g., paresthesias, spasms and cramps) are the most characteristic features of hypocalcemia.

Diagnosis

- Confirm true hypocalcemia: Measure total and ionized calcium
- Serum intact PTH: the best initial study
- · Laboratory findings in hypocalcemia

Findings	Conditions
Low PTH , ↑Phosphate	Hypoparathyroidism (e.g., postsurgical)
High PTH, ↑Phosphate	Hyperphosphatemia
	Pseudohypoparathyroidism
High PTH, ↑Phosphate, ↑Creatinine	Chronic kidney disease
High PTH, ↓ Magnesium	Malabsorption or alcoholism

Management

- Mild and/or chronic hypocalcemia: no symptoms or only mild neuromuscular irritability (e.g., paresthesias): Oral calcium supplementation
- Severe and/or symptomatic hypocalcemia: e.g., tetany, seizures, prolonged QT interval, serum calcium ≤ 7.5 mg/dL (< 1.9 mmol/L)
- ⇒ intravenous **calcium gluconate**, 10ml of 10% solution over 10 minutes. intravenous **calcium chloride** is more likely to cause local irritation
- ⇒ ECG monitoring
- Treatment of the underlying condition
- ⇒ Hypoparathyroidism → Calcium and vitamin D supplementation
- Secondary to loop diuretics: consider discontinue loop diuretic and change medication to thiazides.
- ⇒ Vitamin D deficiency: vitamin D supplementation
- ⇒ Hypomagnesemia-induced hypocalcemia: magnesium supplementation

IV calcium can trigger life threatening arrhythmias in patients simultaneously receiving cardiac glycosides (digoxin or digitoxin).

Daily calcium intake of between 700 and 1200mg should be advised

Magnesium (Mg)

Overview

- Mg is the second most abundant intracellular cation in the body (after potassium)
- 99% of total body magnesium is intracellular or bone-deposited, with only 1% present in the extracellular space.
- Normal plasma magnesium → (0.7-0.9 mmol)
- Dietary magnesium is absorbed by the ileum of the small intestine, stored mainly in the bones, and excreted by the kidneys.

Dietary sources of magnesium

• green vegetables, fruits, fish, fresh meat, and cereals.

Recommended daily intake of magnesium

- Adult females: 280 mg/day normally, increased to 350 mg/day during pregnancy and lactation
- Adult males: 350 mg/day

Magnesium homeostasis

- About **60%** of magnesium in the serum is **free**, whereas 33% is bound to proteins,
- Magnesium status is regulated by the intestines, which control absorption; the kidneys, which control excretion; and bone, which is the major storage site.
- Intestinal absorption and renal excretion are mediated by the selective magnesium channel TRPM6.
- magnesium uptake and release from tissues outside the intestines and kidneys is controlled by TRPM7.
- most of the absorption taking place in the colon.
- Hormones such as glucagon, catecholamines, and parathyroid hormone (PTH) can mobilise magnesium from bone and other tissues.
- hormones such as insulin, antidiuretic hormone (ADH), and thyroid hormone promote magnesium uptake and storage.
- The main controlling factors in magnesium homeostasis → GIT absorption and renal excretion.
 - ⇒ Renal reabsorption
 - the major site of reabsorption is the loop of Henle,
 - Unlike most ions, the majority of magnesium is not reabsorbed in the proximal convoluted tubule (PCT). the thick ascending limb (TAL) of the loop of Henle is the major site of reabsorption (60-70%).
 - In the TAL, magnesium is passively reabsorbed with calcium through paracellular tight junctions
 - Claudins are the major components of tight-junction strands in the TAL, where the reabsorption of magnesium occurs
 - In the distal convoluted tubule (DCT), magnesium is reabsorbed via an active, transcellular process that is thought to involve TRPM6
 - The TRPM6 channel is embedded in the membrane of epithelial cells of large intestine, distal convoluted tubules, lungs, and testes.

Uses for magnesium include:

- polymorphic ventricular tachycardia (torsade de pointes),
- acute asthma
- · prevention/treatment of seizures in pre-eclampsia.
- · Magnesium salts can be given as laxatives

Hypomagnesaemia

Replace magnesium before correcting hypokalaemia.

Hypomagnesaemia prevents potassium absorption

Definition

magnesium below 0.7 mmol/L

Causes

Gastrointestinal

- ⇒ Inadequate intake (e.g., anorexia nervosa, prolonged fasting): the most common cause
- ⇒ Malnutrition
- ⇒ Malabsorption
- ⇒ Gastric bypass surgery, small bowel bypass surgery, short bowel syndrome
- ⇒ Vomiting, nasogastric suction
- ⇒ Acute and chronic diarrhea
- ⇒ Chronic inflammatory bowel disease
- ⇒ Acute pancreatitis
- ⇒ Total parenteral nutrition
- ⇒ Refeeding syndrome

Renal

- ⇒ Diuresis
- ⇒ ATN
- ⇒ Congenital conditions
 - Bartter syndrome
 - Gitelman syndrome
 - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
 - Congenital magnesium wasting

Endocrine

- ⇒ SIADH
- ⇒ Hyperaldosteronism
- ⇒ Hyperparathyroidism
- ⇒ Hyperthyroidism

Intracellular shift

- ⇒ Post myocardial infarction
- ⇒ Post parathyroidectomy
- ⇒ Recovery from diabetic ketoacidosis (K+ and PO₄- also enter cells)
- ⇒ Refeeding syndrome (PO₄- also enters cells),
- ⇒ Acute pancreatitis.

• Drug- induced:

- ⇒ Diuretics
- ⇒ Ciclosporin and cisplatin → trenal reabsorption and ↑renal excretion of Mg²⁺
- \Rightarrow Insulin $\rightarrow \uparrow$ intracellular uptake of Mg²⁺ \rightarrow hypomagnesaemia.
- Antibiotics such as aminoglycosides, gentamicin, and tobramycin inhibit renal reabsorption in the loop of Henle.
- ⇒ cardiac glycosides, Digitalis → †intracellular sodium and calcium → displacement and loss of magnesium.
- ⇒ Amphotericin B
- Colorectal cancer treatment with cetuximab/panitumumab → inhibits extracellular growth factor receptor (EGFR) →
 TRPM6 → hypomagnesemia.
- Omeprazole (PPIs) → ↓ intestinal Mg²⁺ absorption through TRPM6 and produce renal magnesium wasting by an unknown mechanism. hypomagnesaemia → hypoparathyroidism → hypocalcaemia.
 - The reasons for this are unclear, but it may be due to reduced uptake of Mg²⁺ ions in the gut. Omeprazole reduces acid production and raises stomach PH. An acid environment can aid release of metal ions from their binding sites in food molecules which facilitate absorption.

Metabolic acidosis

- ⇔ Osmotic diuresis, which occurs in diabetic ketoacidosis, leads to renal magnesium wasting.
- ⇒ Chronic metabolic acidosis → ↓renal TRPM6 expression in the DCT → ↓ Mg reabsorption →↓ serum Mg.

Hypercalcaemia

- ⇒ Hypercalcemia → activation of calcium-sensing receptor (CaSR) → ↓ Mg reabsorption
- ⇒ Calcium competes with magnesium for uptake in the loop of Henle, and an increase in the filtered calcium load can impair magnesium reabsorption.

Rurne

Chronic alcohol use

· Genetic diseases

- ⇒ Hypomagnesemia with secondary hypocalcemia (HSH):
 - Autosomal recessive
 - caused by mutations in the TRPM6 gene → ↓↓ intestinal magnesium reabsorption→↓↓ serum magnesium → ↓↓ (PTH) → ↓↓ serum calcium levels (hypocalcemia).
 - manifests in early infancy with generalized convulsions refractory to anticonvulsant treatment or with other symptoms of increased neuromuscular excitability, such as muscle spasms or tetany.
 - Laboratory evaluation reveals extremely low serum magnesium and serum calcium levels

Features

General

- lack of appetite.
- Lethargy
- fatique

Neuromuscular hyper-excitability

- muscle weakness including fasciculations
- · changes in personality
- paraesthesia
- tetany
- seizures

Cardiac

- arrhythmias (ECG features similar to those of hypokalaemia) typically QT prolongation.
- exacerbates digoxin toxicity

Electrolytes

- ↓Mg → ↓PTH secretion + ↑PTH resistance → hypocalcaemia
- Hypokalemia (in 40-60%) (↓Mg →↑renal potassium wasting)

Complications

- Cardiac arrest
- Seizures

Investigation

- Serum magnesium level do not accurately reflect total body magnesium status. only 1% of magnesium is found in the extracellular fluid
- There is no accurate laboratory test to determine total body magnesium
- Urine Mg excretion is a useful guide. When there is inadequate intake or malabsorption, the kidneys would normally conserve Mg, giving urine Mg concentrations <7 mmol/24 hours.
 The reference range is around 2-7 mmol/24 hours.

Treatment

- Repletion should be considered in all patients with symptoms consistent with hypomagnesemia, including patients with normal serum magnesium levels.
- <0.4 mmol/l
 - intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours
- >0.4 mmol/l
 - ⇒ oral magnesium salts (10-20 mmol orally per day)
 - ⇒ diarrhoea can occur with oral magnesium salts

Parenteral administration of magnesium can reduce serum calcium levels, which can worsen preexisting hypocalcemia.

Hypermagnesaemia

Overview

- Mg above the reference range 0.7-1.5 mmol/L.
- Hypermagnesaemia is much less common than hypomagnesaemia and is often iatrogenic in cause.

Causes

• latrogenic:

- ⇒ Treatment with magnesium sulphate to prevent/treat seizures in patients with eclampsia or pre-eclampsia
- ⇒ Treatment with Mg containing antacids
- ⇒ Use of citrate-glucuronic acid solutions to dissolve renal calculi either through bladder irrigation or via a nephrostomy tube
- ⇒ Over-zealous IV treatment of hypomagnesaemia
- ⇒ Chronic use of Mg-containing enemas.
- Other causes:
 - ⇒ Acute or chronic renal failure
 - release of Mg from tissues,
 - Mg in dialysate,
 - Mg in phosphate binding drugs
 - ⇒ Familial hypocalciuric hypercalcaemia.

Lithium can cause hypermagnesaemia

Features

- Mild hypermagnesaemia (1.5-2.5 mmol/L) symptoms uncommon
- Moderate hypermagnesaemia (2.5-5.0 mmol/L) symptoms develop including hypotension, prolonged PR and QRS intervals on ECG, areflexia
- Severe hypermagnesaemia (>5.0 mmol/L) at risk of respiratory paralysis through inhibition of acetylcholine release and cardiac arrest.

Treatment

- If mild/moderate and iatrogenic, often it is enough to identify and stop the cause.
- In an emergency, dialysis or administration of IV calcium glucuronate (10 ml of 10%) will reduce the effects of hypermagnesaemia.

Vitamin D (calciferol)

Sources

- Vitamin D2 (ergocalciferol): plants
- Vitamin D3 (cholecalciferol): dairy products, can be synthesised by the skin from sunlight (the main natural source).

Vitamin D synthesis

- Liver: cholesterol → 7-dehydrocholesterol (provitamin D3) Enzyme: cholesterol dehydrogenase
- 2. Skin
 - ⇒ Storage of 7-dehydrocholesterol
 - ⇒ Cleavage of 7-dehydrocholesterol via irradiation with UV light → cholecalciferol (in the stratum basale)
- 3. Liver: hydroxylation of cholecalciferol to 25-hydroxyvitamin D (25-OH D3, calcidiol)
- **4. Kidneys**: 1α-hydroxylase hydroxylates 25-hydroxyvitamin D → 1,25-dihydroxyvitamin D

Transport to target cells: vitamin D-binding protein (DBP)

Storage: as 25-hydroxycholecalciferol, mainly in adipose tissue (25-OH D3)

Active form: 1,25-dihydroxyvitamin D (1,25-(OH)2 D3, calcitriol)

Regulation of vitamin D synthesis: via regulation of 1α-hydroxylase activity in proximal convoluted tubule

- \downarrow Calcium, \downarrow phosphate, and ↑ PTH → ↑ 1α-hydroxylase activity → ↑ 1,25-dihydroxyvitamin D biosynthesis
- ↑ Calcium, ↑ phosphate, and ↑ 1,25-dihydroxyvitamin D (feedback inhibition) $\rightarrow \downarrow 1\alpha$ hydroxylase activity → ↓ 1,25-dihydroxyvitamin D biosynthesis

Functions

- †plasma calcium and plasma phosphate
 - ⇒ ↑ intestinal absorption of magnesium and phosphate
 - vitamin D → ↑calbindin (an intestinal transporter of calcium) → ↑calcium absorption from the small intestine.
 - ⇒ ↑ renal tubular reabsorption of calcium and phosphate
- ↑ osteoclastic activity
- †calcium deposition in the extracellular matrix of bone.
- Suppression of synthesis of type 1 collagen. This is balanced by upregulation of osteocalcin, the balance of these changes is an increase in bone mineralisation.
- Vitamin D is recognised to modulate cytokine production and may have a role in the treatment of inflammatory disorders in the future. One example is decreased production of IL6 in response to vitamin D supplementation.

Vitamin D deficiency

Definition

serum 25-hydroxyvitamin D <50 nanomole/L (<20 nanograms/mL).

Epidemiology

- The most common nutritional deficiency worldwide
- In UK around 5 % of adults and 8 24% of children may have low vitamin D status.

Features and complications:

- · Rickets: seen in children
 - ⇒ Radiographs of the limbs will demonstrate epiphyseal widening with metaphyseal fraying.
- Osteomalacia: seen in adults
 - ⇒ It classically presents in the female Asian population whose clothing offers little exposure to sunlight.
 - Proximal myopathy is often a presenting feature of osteomalacia
 - ⇒ increasing falls
 - ⇒ The phosphate and calcium are usually low normal, and the alkaline phosphatase is
 - ⇒ Elevated PTH (secondary hyperparathyroidism to maintain the normal calcium.)
- Symptoms of hypocalcemia (e.g., tetany)

Diagnosis

Measurement of serum 25-OH vitamin D is the best way of estimating vitamin D status.

Serum Vit D	Response
Optimal: > 75nmol/l	Nothing
Adequate: 5075nmol/I	provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet
Insufficiency: 30-49nmol/l	treatment is advised in patients with fragility fracture, osteoporosis, symptoms suggestive of vitamin D deficiency, reduced exposure to sunlight, raised PTH, conditions associated with malabsorption
Deficiency: < 30nmol/l	treatment recommended

Treatment (loading doses followed by regular maintenance therapy).

- · Loading dose:
 - ⇒ a total of approximately 300,000 IU vitamin D, given either as separate weekly or daily doses over 6 to 10 weeks
 - Regimes include:
 - ❖ 50,000 IU given weekly over 6 weeks **OR**
 - ❖ 4,000 IU given daily over 10 weeks
- Maintenance dose
 - ⇒ vitamin D in doses equivalent to 800–2000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at higher doses.
- · Assess his calcium intake:
 - ⇒ co-prescription of a calcium supplement may be required if the nutritional intake is less than 800mg daily.
 - ⇒ In patients with good calcium intake and normal serum calcium, giving oral calcium may lead to adverse cardiovascular outcomes, due to accelerated tissue and vascular calcification.

Adverse effects

- Vitamin D toxicity (hypercalciuria and hypercalcemia)
 - ⇒ Causes
 - Oversupplementation
 - Granulomatous disorders (e.g., sarcoidosis): due to increased 1α-hydroxylase activation in epithelioid macrophages → increased 1,25-dihydroxyvitamin D synthesis
 - ⇒ Clinical features
 - Hypercalcemia, hypercalciuria
 - Loss of appetite
 - Stupor

Vitamin D supplementation

- The following groups should be advised to take vitamin D supplementation:
 - ⇒ all pregnant and breastfeeding women should take a daily supplement containing 10μg of vitamin D
 - ⇒ all children aged 6 months 5 years. Babies fed with formula milk do not need to take a supplement if they are taking more than 500ml of milk a day, as formula milk is fortified with vitamin D

- ⇒ adults > 65 years
- ⇒ Current NOS guidelines recommend that all people over the age of 65 take a daily supplement containing 10mcg (400 IU) of vitamin D.
- ⇒ people who are not exposed to much sun should also take a daily supplement

Testing for vitamin D deficiency:

- ⇒ Advised in the following situations (NOS guidelines)
 - patients with bone diseases that may be improved with vitamin D treatment e.g. known osteomalacia or Paget's disease
 - patients with bone diseases, prior to specific treatment where correcting vitamin deficiency is appropriate e.g, <u>prior to intravenous zoledronate or</u> denosumab
 - patients with <u>musculoskeletal symptoms</u> that could be attributed to vitamin D deficiency e.g. bone pain? osteomalacia
- ⇒ Testing for vitamin D deficiency is not necessary in the following:
 - Patients with osteoporosis → should always be given calcium/vitamin D supplements
 - People at higher risk of vitamin D deficiency → should be treated anyway

Phosphate

Phosphate overview

- Normal range: 3.0–4.5 mg/dL (1.0–1.5 mmol/L)
- **Daily phosphate requirement: 1-2 g**, but typical intake is higher, 3-6 g, mostly through meats and grains.
- Foods that are rich in phosphate include: dairy products, (Cheddar cheese), fibre rich foods, chocolate, and processed meats.
- Absorption occurs mainly in the jejunum
- Storage
 - ⇒ 85% of the body's phosphate is found in the bone matrix.
 - Outside of bone, phosphate is mainly found in the intracellular space (esp. in soft tissue cells).

Importance

⇒ Component of many important molecules, including creatine phosphate, membrane phospholipids, DNA, ATP/ADP, 2,3-DPG, and NADP

Excretion

- ⇒ All circulating phosphate is not bound to proteins, so all of it can be filtered, and the kidney is the only way it is excreted.
- ⇒ The majority (70%) of filtered phosphate is reabsorbed by type 2a sodium phosphate cotransporters located on the apical membrane of the renal proximal tubule. Impaired expression or function of these transporters is associated with nephrolithiasis.
- ⇒ kidney failure leads to high serum phosphate levels (hyperphosphatemia) that can cause secondary bone fractures and bone pain (renal osteodystrophy).

Phosphate homeostasis

- ⇒ Vitamin D stimulates intestinal absorption and release of phosphate from bones.
- PTH stimulates renal phosphate excretion by inhibiting its reabsorption in the kidneys.

Hypophosphataemia

Definition

• serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L).

Causes and Mechanisms: The 4 major mechanisms of hypophosphataemia are:

- 1. Redistribution of extracellular phosphate into cells (Transcellular phosphate shifts)
 - ⇒ hyperventilation → respiratory alkalosis → activating phosphofructokinase → moves phosphate into cells → stimulates intracellular glycolysis.
 - ⇒ Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced.
 - ⇒ Any cause of hyperventilation (eg, sepsis, anxiety, pain, heatstroke, alcohol withdrawal, diabetic ketoacidosis [DKA], hepatic encephalopathy, salicylate toxicity, neuroleptic malignant syndrome [NMS]) can precipitate hypophosphatemia.
- 2. Decreased intestinal absorption
 - ⇒ chronic diarrhea
 - ⇒ malabsorption syndromes
 - ⇒ severe vomiting
 - ⇒ nasogastric (NG) tube suctioning
 - ⇒ Alcohol use disorder
- 3. Increased urinary loss. (the most common cause of hypophosphatemia)
 - ⇒ primary and secondary hyperparathyroidism.
 - ⇒ Osmotic diuresis, such as seen in hyperosmolar hyperglycemic syndrome (HHS)
 - ⇒ Fanconi syndrome (proximal tubule dysfunction)
 - ⇒ X linked hypophosphataemic rickets
 - ⇒ Oncogenic hypophosphataemic osteomalacia
- 4. Pseudohypophosphatemia

What types of medications can impair gut phosphate absorption?

• Antacids, specifically those that are aluminium or magnesium based.

Fanconi syndrome is a genetic disorder of the renal proximal tubule whereby various substances—including glucose, bicarbonate, potassium, and phosphate—are unable to be reabsorbed, causing their loss in the urine. It can lead to growth defects and bone disorders.

Features

- · Cardiac: arrhythmias
- Musculoskeletal: Osteomalacia (fatigue, muscle pain and weakness, respiratory muscle weakness). severe hypophosphatemia (< 2.5 mg/dL) is associated with elevated serum alkaline phosphatase.
- Neurological: paresthesia, altered mental state, seizures
- Hematological: anemia, haemolysis, and thrombocytopenia
- Impaired immunity (WBC and platelet dysfunction)
- Hypophosphatemia →↓ 2,3-diphosphoglycerate (2,3-DPG), (a glycolytic intermediate in red blood cell metabolism that has higher affinity for deoxygenated hemoglobin than for

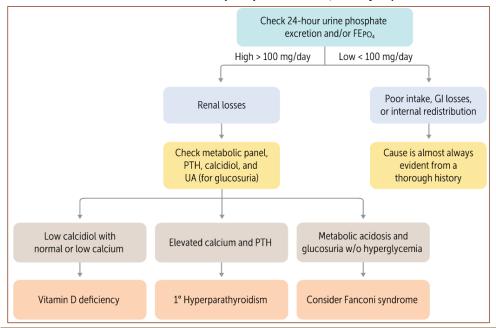
oxygenated hemoglobin) $\rightarrow \uparrow$ affinity of hemoglobin (Hb) for oxygen \rightarrow shifting the dissociation curve to the left \rightarrow impairing red blood cell release of oxygen to tissues

Why is hypophosphatemia a problem in patients with respiratory failure?

 Limited release of oxygen to tissues because of 2,3-DPG depletion and respiratory muscle weakness.

Diagnosis and evaluation

Summary of the clinical work-up for a patient with hypophosphatemia (FEpo4 indicates fractional excretion of phosphate and UA, urinalysis).



MRCPUK- part-1-Sep 2017: what is the mechanism of Hypophosphataemia during treatment of DKA?

Shift from extracellular to intracellular space

MRCPUK-part-1-Sep 2017: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission ?

- Shift from extracellular to intracellular space. The alcoholic patient often has chronic
 phosphate depletion, and, after admission to the hospital, is prone to severe
 hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.
 - Two factors may contribute to this shift:
 - I.V therapy with dextrose-containing solutions or refeeding → ↑Glucose
 → ↑ insulin release → ↑ phosphate uptake by the cells
 - alcohol withdrawal → hyperventilation → acute respiratory alkalosis → intracellular alkalosis → stimulates intracellular phosphofructokinase →↑ glycolysis → movement of phosphate into cells.

Hyperphosphataemia

Causes and mechanisms

- Decreased phosphate excretion (Renal failure, Hypoparathyroidism)
- Increased tissue breakdown (e.g., tumor lysis syndrome, rhabdomyolysis, crush injury) → shifts intracellular phosphate to extracellular space
- Increased phosphate intake (e.g., phosphate-containing enemas)
- Pseudohypoparathyroidism
- Vitamin D intoxication
- Bisphosphonates (have also been shown to cause hypophosphatemia)
- •

Features

- Often asymptomatic
- High PO43- levels cause the formation of an insoluble compound with calcium, which can lead to:
 - ⇒ Hypocalcemia
 - ⇒ Nephrolithiasis
 - ⇒ Calcifications in the skin
- ↓calcium + ↑ phosphate levels seen in:
 - ⇒ renal failure, hypoparathyroidism, and pseudohypoparathyroidism
- ↑calcium + ↑phosphate seen in:
 - ⇒ vitamin D intoxication (↓PTH + ↑ vitamin D)
 - ⇒ milk-alkali syndrome (↓PTH + ↓vitamin D)

Management

- Treat the underlying cause.
- Discontinue phosphate intake (dietary or medication).
- Give phosphate binders (e.g., aluminium hydroxide, calcium carbonate).
- Consider dialysis (especially in severe cases of hyperphosphatemia in patients with renal failure).

Hyperparathyroidism

Classification

Туре	PTH	Serum Ca	Serum Phos	Causes
Primary	Normal	High	low	parathyroid adenoma
Secondary	High	Normal or low	High	CRF → ↓ vit D → ↓ gut Ca ²⁺ absorption → ↓ Ca2+ → ↑PTH CRF → ↓ phosphate excretion → hyperphosphatemia. Causes of ↓ Ca2+: • renal failure (most common) • insufficient vit D, • insufficient Ca2+ in the diet, • excessive Mg2+ in the diet
Tertiary	High	High	High	hyperplasia of the glands, and loss of response to ca2+. occurs after years of secondary hyperparathyroidism PTH is raised, calcium is raised and so is phosphate, whilst eGFR is significantly deceased

Primary hyperparathyroidism

Mechanism of PTH effects:

- Reabsorbs calcium at distal tubule
- Excretes phosphate at proximal tubule
 - ⇒ A mnemonic to remember this is **PTH** = "Phosphate Trashing Hormone."
- Activates vitamin D from 25 to the 1,25 dihydroxy form
 - increased activity of renal 1-α-hydroxylase (which converts inactive 25-hydroxycholecalciferol into active 1, 25-dihydroxycholecalciferol).
- Reabsorbs both calcium and phosphate from bone

In exams primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level.

Pathophysiology

 PTH indirectly stimulates osteoclasts by binding to its receptor on osteoblasts, inducing RANK-L and M-CSF synthesis

Epidemiology

- · the most common cause of hypercalcemia
- occurs in 0.1% of the population
- · most commonly found in women between 50 and 60 years of age
- Two to three times more common in women than men.

Causes

- 80%: solitary adenoma
- 4%: multiple adenoma
- 15%: hyperplasia
- 1%: carcinoma (PTH is grossly elevated)

Pathophysiology: overproduction of Parathyroid hormone (PTH) by parathyroid chief cells

- Effect of PTH on bone → ↑ bone resorption → ↑ release of calcium phosphate → ↑ calcium levels
 - □ Induces RANKL expression in osteoblasts → binding of RANKL to RANK on osteoclasts → activation of osteoclasts
 - ⇒ Induces IL-1 expression in osteoblasts → activation of osteoclasts
- **Effect of PTH on the kidneys** → ↑ phosphate excretion (phosphaturia)

Features: 'bones, stones, abdominal groans and psychic moans'

- . The majority of patients are asymptomatic.
- · Cardiovascular system
 - ⇒ Arterial hypertension → Left ventricular hypertrophy
 - ⇒ Shortened QT interval on the ECG
- Kidney
 - ⇒ Nephrolithiasis, nephrocalcinosis → abdominal/flank pain (Stones)
 - ⇒ Polyuria, polydipsia (thrones)
- Musculoskeletal system (bones)
 - ⇒ Bone, muscle, and joint pain
 - ⇒ Pseudogout
- GIT (abdominal groans)
 - \Rightarrow Nausea, constipation (\uparrow calcium $\rightarrow \downarrow$ smooth muscle contraction \rightarrow constipation)
 - ⇒ Gastric or duodenal ulcers

- ⇒ Acute pancreatitis
- Psychological symptoms: depression, fatigue, anxiety, sleep disorders (psychiatric overtones)

"Stones, bones, abdominal groans, thrones, and psychiatric overtones!"

Associations

- Hypertension
- Multiple endocrine neoplasia: MEN I and II
 - ⇒ The association of primary hyperparathyroidism and a gastrinoma would suggest a diagnosis of multiple endocrine neoplasia type 1.
- Osteitis fibrosa cystica
 - ⇒ The cystic bone spaces seen on radiography are most likely osteitis fibrosa cystica, a condition in which brown, fibrous tissue fills bone cysts.
 - Consist of osteoclasts and hemosiderin (hemosiderin accumulates in bone cysts as a result of hemorrhage)
 - ⇒ Subperiosteal thinning

Investigations

- · Raised calcium, low phosphate
 - ⇒ Hypophosphataemia is due to → reduced renal reabsorption of phosphate.
- PTH may be raised or normal (A high or even normal PTH concentration in the presence of hypercalcaemia would support the diagnosis of hyperparathyroidism)
- · technetium-MIBI subtraction scan
- Technetium (99mTc) sestamibi scanning
 - ⇒ The most sensitive and specific technique for tumor localization
 - ⇒ Only performed prior to surgery to determine the exact location of the abnormal glands
- 24 hour urinary calcium may be useful if used in comparison to the serum calcium in order to distinguish familial hypocalciuric hypercalcaemia from primary hyperparathyroidism.
- Urinary cAMP increases, because PTH works on the G protein pathway, Gs, which uses cAMP as a secondary messenger.

The effect of PTH on calcium and phosphate

Mechanism	calcium	Phosphate
Excretion by kidneys	Low	High
Absorption from gut	High	High
Absorption from bone	High	High
Net Serum concentration	High	Low

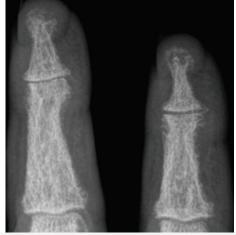
The PTH level in primary hyperparathyroidism may be normal

Phosphate is usually elevated or normal in bone metastases (this clue could differentiate primary hyperparathyroidism from cancer metastases)

Treatment

- Surgery
 - ⇒ In cases of solitary adenoma: Only the respective gland is removed.
 - ⇒ In cases of hyperplasia: All four glands are removed.
- · Parathyroidectomy: Indications:
 - ⇒ **Symptomatic** patient (definitive signs and symptoms of hypercalcaemia- such as proximal weakness, gait disturbance, hyper-reflexia)
 - **⇒** Asymptomatic + one of the following:
 - Age less than 50
 - Markedly elevated corrected serum calcium (above 3 mmol/l),
 - Serum albumin-adjusted calcium greater than 0.25 mmol/L above the normal range
 - 24 hour total urinary calcium excretion greater than 10 mmol (400 mg)
 - Renal stones, or presence of nephrocalcinosis on ultrasound or CT.
 - Impaired renal function, creatinine clearance reduced by 30% or more
 - Presence of osteoporosis or osteoporotic fracture (Bone mineral density T-score less than -2.5 at any site)
 - Unwillingness of patient to follow advice of medical surveillance. (Patient request; adequate follow-up unlikely).
- Complication of parathyroidectomy : hungry bone syndrome
 - occur after parathyroidectomy if the hyperparathyroidism has been long standing.
 - ⇔ Characterized by severe hypocalcemia despite a normal or increased serum concentration of parathyroid hormone
 - ⇒ Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half-life) and the osteoclast activity is subsequently diminished, and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'.
 - ⇒ In addition to hypocalcemia, patients can also develop hypophosphatemia, hypomagnesemia, and hyperkalemia.
 - ⇒ x-ray changes very similar to metastatic lytic lesions if left untreated.





Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal pharyngeal tufts (acro-osteolysis) and sub-periosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

Secondary hyperparathyroidism

Secondary hyperparathyroidism (sHPT): Hypocalcemia results in reactive hyperplasia of the parathyroid glands, develops due to decreased levels of calcium in the blood (reactive HPT).→ overproduction of PTH.

Definition

- Elevation of parathyroid hormone (PTH) in response to hypocalcemia induced by phosphate retention and reduced calcitriol synthesis as a consequence of reduced renal function
- Because 2° HPT is a compensatory mechanism of the parathyroid glands, it commonly resolves with normalization of calcium and phosphorus homeostasis (eg, renal transplantation).

Causes

- Chronic kidney disease (most frequent cause)
- Malnutrition
- Vitamin D deficiency (e.g., reduced exposure to sunlight, nutritional deficiency, liver cirrhosis)

Secondary hyperparathyroidism is due to the overproduction of PTH secondary to low calcium. Usually, this is seen in chronic renal failure or vitamin D deficiency.

Pathophysiology

- Secondary hyperparathyroidism: ↓ calcium and/or ↑ phosphate blood levels → reactive hyperplasia of the parathyroid glands → ↑ PTH secretion
- Chronic kidney disease → impaired renal phosphate excretion → ↑ phosphate blood levels→ ↑ PTH secretion
- In addition, CKD → ↓ biosynthesis of active vitamin D → ↓ intestinal calcium resorption and ↓ renal calcium reabsorption → hypocalcemia → ↑ PTH secretion

Feature

- ↓ Ca²⁺, ↑ serum phosphate, ↑PTH
- † alkaline phosphatase (renal osteodystrophy).

Management

- Dietary phosphate restriction
 - ⇒ In patients with chronic kidney disease (CKD), dietary phosphorus should be restricted to 800 to 1000 mg/day.
- Calcium and vitamin D replacement
- **Phosphate binders** (sevelamer): indicated when phosphorus levels are high. If phosphorus or PTH levels cannot be controlled despite dietary phosphorus restriction.
 - ⇒ Mechanism of action: binds phosphate in the gut (sevelamer is nonabsorbable) → ↓ phosphate absorption → ↓ serum phosphate → ↓ PTH
 - ⇒ Indication: hyperphosphatemia caused by chronic kidney disease
- Calcimimetics (e.g., cinacalcet)
 - Mechanism of action: modulation of calcium-sensitive receptor (CaSR) in parathyroid glands → ↑ sensitivity of the receptor to circulating Ca2+ → inhibition of PTH release

⇒ Indication

- Primary hyperparathyroidism after failed parathyroidectomy
- Hypercalcemia in hemodialysis patients with secondary hyperparathyroidism due to CKD
- Parathyroid carcinoma with hypercalcemia
- Parathyroidectomy is reserved for severe secondary hyperparathyroidism resistant to medical management (on maximal doses of cinacalcet, and still, the PTH level is high).
 - ⇒ bone pain, fracture, or calciphylaxis.
- . Renal transplant is the optimal treatment for secondary HPT.

Unlike primary hyperparathyroidism, secondary hyperparathyroidism is treated medically by correcting vitamin D deficiency.

Tertiary hyperparathyroidism

Epidemiology

 tertiary HPT requiring surgical intervention occurs in 1–5% of patients with HPT after undergoing kidney transplant.

Pathophysiology

Chronic renal disease → longstanding secondary hyperparathyroidism → hyperplasia of all four glands → refractory and autonomous secretion of PTH (secrete PTH regardless of Ca2+ level) → hypercalcemia.

Causes

· Caused by persistent secondary HPT

Management

- treatment of patients with tertiary HPT is surgical.
- medical treatment is not curative and, generally, not indicated.
- Cinacalcet should be only offered in patients who are unfit for surgery.

Hypoparathyroidism

Causes

- Postoperative: most commonly occurs as the result of accidental injury to parathyroids (or their blood supply) during thyroidectomy, parathyroidectomy, or radical neck dissection
- · Autoimmune: second most common cause
- Infiltration of parathyroid gland: (e.g. Wilson disease, hemochromatosis)
- Radiation-induced destruction
- Gram-negative sepsis
- · Toxic shock syndrome
- HIV infection
- Congenital: Parathyroid gland aplasia or hypoplasia (DiGeorge syndrome)
- Frequency increased in alcoholics, particularly in association with hypomagnesaemia.
 - ⇒ Alcohol → Hypercalciuria & hypermagnesuria → hypocalcemia and

Features

- Symptoms of hypocalcemia, such as tetany (see hypocalcemia topic)
- Hypocalcemia with low or inappropriately normal PTH
- Hyperphosphatemia

Treatment

- · Treat underlying disease
- Calcium and vitamin D supplementation
- Recombinant human PTH can reduce the amount of supplemental calcium and vitamin D required.

Pseudohypoparathyroidism

Definition

 end-organ (i.e., bones and kidneys) resistance to parathyroid hormone (PTH) despite sufficient PTH synthesis due to a defective Gs protein α subunit

Epidemiology

• Occurs twice as frequently in females as in males.

Inheritance

- · Autosomal dominant
- Inherited from the mother (GNAS gene imprinting)

Pathophysiology

mutations in GNAS1 → Defective Gs protein α subunit → missing activation of adenylate cyclase when PTH binds to Gs → resistance to PTH in kidney and bone tissue

Types

- type I: there is a complete receptor defect
- type II: the cell receptor is intact.

Features

- Albright hereditary osteodystrophy (AHO)
 - ⇒ Short stature, Round face
 - ⇒ Obesity
 - ⇒ Brachydactyly of the 4th and 5th fingers (short fourth and fifth metacarpals)
 - ⇒ Intellectual disability
 - ⇒ Subcutaneous calcification
- Symptoms related to low calcium and high phosphate levels: Seizures, Numbness, tetany, Cataracts, Dental problems

Diagnostics

- Persistent hypocalcemia despite ↑ PTH levels
- ↑ Phosphate levels
- Alkaline phosphatase: high

- Diagnosis is made by measuring <u>urinary cAMP</u> and <u>phosphate</u> levels following an infusion of PTH.
 - ⇒ In <u>hypoparathyroidism</u> this will cause an increase in both cAMP and phosphate levels.
 - ⇒ In <u>pseudohypoparathyroidism type I</u> neither cAMP nor phosphate levels are increased
 - ⇒ whilst in **pseudohypoparathyroidism type II** only cAMP rises.

Radiographic features

- Musculoskeletal manifestations
 - ⇒ soft tissue calcification
 - ⇒ exostoses: short metaphyseal or more central and perpendicular to long axis of bone
 - ⇒ broad bones with coned epiphyses
- CNS / head and neck manifestations
 - ⇒ basal ganglia calcification
 - ⇒ sclerochoroidal calcification
 - ⇒ deep white matter calcification

Management

Calcium and vitamin D supplementation

Pseudo pseudohypoparathyroidism

 Similar phenotype to pseudohypoparathyroidism but inherited from the father and associated with normal biochemistry (normal calcium, PTH, and phosphate)

Pseudohypoparathyroidism is when the defect is inherited from the mother while pseudo pseudohypoparathyroidism is inherited from the father.

Osteomalacia

The symptoms of proximal bone pain with hypocalcaemia and low phosphate suggest a diagnosis of osteomalacia

 $\downarrow \downarrow$ Ca $\downarrow \downarrow$ P $\downarrow \downarrow$ vit D + $\uparrow \uparrow$ ALP → osteomalacia

Definition

- Defective mineralization of osteoid, most commonly due to vitamin D deficiency.
- Normal bony tissue but decreased mineral content.
- If occurred in children (growth plates have not fused) called rickets.

Pathophysiology

- ↓vitamin D →↓serum Ca2+ →↑PTH secretion →↓serum phosphate → impaired mineralization.
- Hyperactivity of osteoblasts →↑ALP.

Risk factors

- Lack of sun exposure, e.g. people who <u>spend more time inside</u> and people who are <u>cover</u> themselves up (so that cholesterol cannot be converted to vitamin D in the skin).
- Ethnic groups who are dark-skinned
- Asians who eat chapattis (as the phytic acid in the chapattis chelates vitamin D and calcium)

Causes

- · Vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- · Vitamin D resistant; inherited
- Renal failure
- · Liver disease, e.g. cirrhosis
- Drug induced e.g. anticonvulsants
- Mercury poisoning or any heavy metal poisoning causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.

Features

- Bone pain, particularly around the hips and lower back
- · Pathologic fractures
- Muscle tenderness
- Proximal myopathy → Waddling gait and difficulty walking
- · Symptoms of hypocalcemia

Investigation

- ↓ Calcium and ↓ phosphate
- ↑ Alkaline phosphatase and ↑ PTH
- x-ray:
 - ⇒ children cupped, ragged metaphyseal surfaces → Rickets
 - ⇒ adults Looser zones (pseudofractures): transverse bands of radiolucency indicating defective calcification of osteoid (Linear areas of low density)

Differential diagnoses

- Malignancy
- Osteoporosis
- · Paget disease of the bone

Treatment

- Vitamin D deficiency: administration of vitamin D
- Defective vitamin D metabolism or vitamin D-independent forms: treatment of underlying disease

May 2013 exam: A 58-year-old woman C/O aches and pains in her bones. Generally weak and lethargic. low calcium, phosphate and vitamin D levels combined with a raised alkaline phosphatase and parathyroid hormone level. What is the most appropriate management?

→ Start vitamin D3 supplementation (Δ **→** osteomalacia)

Osteopetrosis

Overview

- · also known as marble bone disease
- rare disorder of <u>defective osteoclast</u> <u>function</u> resulting in failure of normal bone resorption
- · results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common.
- · calcium, phosphate and ALP are normal
- · stem cell transplant and interferon-gamma have been used for treatment

Osteoporosis

In osteoporosis, there is decreased bone mass, but mineralization is normal.

Definition

- Loss of cortical bone mass which leads to bone weakness and increased susceptibility to fractures
- Bone mineral density (BMD) = (T-score equal to or less than -2.5).
- Normal bone mineralization and lab values (serum Ca2+ and PO4).

Causes

- Primary osteoporosis (most common form)
 - ⇒ **Type I** (postmenopausal osteoporosis): postmenopausal women
 - Estrogen stimulates osteoblasts and inhibits osteoclasts.
 - ↓estrogen levels following menopause →↑bone resorption.
 - ⇒ Type II (senile osteoporosis): gradual loss of bone mass as patients age (especially > 70 years)
 - ⇒ Idiopathic osteoporosis
 - Idiopathic juvenile osteoporosis
 - Idiopathic osteoporosis in young adults
- Secondary osteoporosis
 - ⇒ Drug-induced/iatrogenic
 - Most commonly due to systemic long-term therapy with corticosteroids (e.g., in patients with autoimmune disease)
 - Anticonvulsants (e.g., phenytoin, carbamazepine)
 - L-thyroxine
 - Anticoagulants (e.g., heparin)
 - Proton pump inhibitors
 - glitazones
 - Aromatase inhibitors (e.g., anastrozole, letrozole): used for breast cancer in postmenopausal women, converts androgens into estrogens.
 - Immunosuppressants (e.g., cyclosporine, tacrolimus)
 - ⇒ Endocrine/metabolic: hypercortisolism, hypogonadism, hyperthyroidism, hyperparathyroidism, renal disease
 - ⇒ Multiple myeloma
 - ⇒ Excessive alcohol consumption
 - ⇒ Immobilization

Risk factors

- **female sex** : ♀ > o (~ 4:1)
- Advancing age
- Family history of osteoporotic fracture
- Low body mass index
- History of glucocorticoid use
- Rheumatoid arthritis
- Current smoking
- Malabsorption (e.g. Coeliac's), malnutrition (e.g., a vegan diet low in calcium and vitamin D), anorexia
- Premature menopause (<45 years) (Early menarche and late menopause are associated with reduced risk of fracture)

Feature

- Asymptomatic (osteoporosis in the absence of fracture, does not cause pain).
- Pathological fractures that are caused by everyday-activities (e.g., bending over, sneezing) or minor trauma (e.g. falling from standing height)
 - □ Common locations: vertebral (most common) > femoral neck > distal radius (Colles fracture) > other long bones (e.g., humerus)
 - ⇒ Vertebral compression fractures
 - Commonly asymptomatic but may cause acute back pain and possible point tenderness without neurological symptoms
 - Multiple fractures can lead to decreased height and thoracic kyphosis.

Diagnosis

- DXA (dual-energy x-ray absorptiometry) scan
 - Definition: a noninvasive technique that calculates bone mineral density (BMD) by using two x-ray beams
 - ⇒ **Measurement sites:** femoral neck and lumbar spine (femoral neck is the preferred site because of its higher predictive value for fracture risk)
 - ⇒ Indications
 - General recommendation for women ≥ 65 years and men ≥ 70 years (onetime screening test)
 - In younger individuals, if additional risk factors are present: e.g., prolonged glucocorticoid use, low BMI (< 21 kg/m2), alcohol use, smoker, amenorrhea
 - ⇒ **Results:** T-score is defined as the difference in standard deviations between the patient's BMD and the BMD of a young adult female reference mean.
 - Osteoporosis: T-score ≤ -2.5 SD
 - Osteopenia: T-score of -1 to -2.5 SD
 - ⇒ Repeating a DXA scan
 - DXA scans are of limited value in assessing response to treatment.
 - Review DXA 2-5 years from previous scan if it is likely to influence management
- Plain radiography
 - ⇒ If osteoporosis is diagnosed: Radiographic assessment of the whole skeletal system is recommended, particularly if a fracture is already suspected or height loss has occurred.
 - ⇒ Increased radiolucency is detectable in cortical bones once 30–50% of bone mineral has been lost
 - ⇒ Osteoporosis can be diagnosed if vertebral compression fractures are present; commonly an incidental finding because such fractures are typically asymptomatic

- Blood tests: Normal serum calcium, phosphate, and parathyroid hormone (PTH) levels
- Investigations for secondary causes (e.g. osteomalacia, myeloma)
- · Assess the risk of subsequent fractures;
 - ⇒ fracture risk assessment tools (FRAX or Q Fracture)
 - ⇒ The use of FRAX for fracture risk assessment is preferred

Osteoporosis diagnosis according to the WHO and International Osteoporosis Foundation criteria:

diagnosis	T score	definition
normal	(≥ −1)	hip BMD greater than the 1 SD below the young adult reference mean
osteopaenia	(−1 to −2.5)	hip BMD between 1 and 2.5 DS below the young adult reference mean
osteoporosis	(≤ −2.5)	hip BMD 2.5 SD or more below the young adult reference mean
Severe osteoporosis	(≤ -2.5 PLUS fracture)	hip BMD 2.5 SD or more below the young adult reference mean + one or more fragility fractures

Osteoporosis is diagnosed if T-score ≤ -2.5 SD and/or a fragility fracture is present.

Glucocorticoid-induced osteoporosis

Overview

- Steroids cause osteoporosis by:
 - ⇒ bone resorption.
 - ⇒ ↓ calcium absorption from the gut,
 - ⇒ ↑↑urinary calcium excretion,
- · The dose?
 - ⇒ The risk ↑↑ with prednisolone 7.5mg a day for 3 or more months.

Management of patients at risk of corticosteroid-induced osteoporosis

- The **RCP guidelines** divide patients into two groups.
 - \Rightarrow age > 65 years **or** H/O previously fragility fracture \rightarrow give bone protection.
 - Fragility fracture defined by The WHO as resulting from a mechanical force equivalent to a fall from standing height or less which should not ordinarily cause a fracture.
 - ⇒ age < 65 years → bone density scan

T score	Management
Greater than 0	Reassure
Between 0 and -1.5	Repeat bone density scan in 1-3 years
Less than -1.5	Offer bone protection

- The first-line treatment is alendronate and risedronate. Patients should also be calcium and vitamin D replete.
- National Osteoporosis Guideline Group (NOGG) 2017 (UK):

- ⇒ Women and men age ≥70 years with a previous fragility fracture or taking high doses of glucocorticoids (≥7.5 mg/day prednisolone), should be considered for bone protective therapy.
- ⇒ In other individuals fracture probability should be estimated using FRAX
 - Bone-protective treatment should be started at the onset of glucocorticoid therapy in individuals at high risk of fracture.

Osteoporosis: assessing fracture risk

Osteoporosis in a man - check testosterone

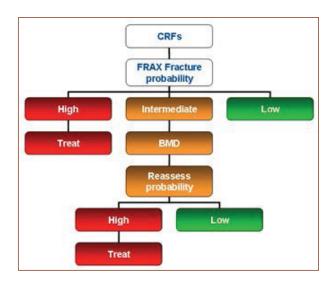
Who should be assessed for fragility fracture?

- All women aged ≥ 65 years and all men aged ≥ 75 years.
- Younger patients + presence of risk factors, such as:
 - ⇒ previous fragility fracture
 - ⇒ current use or frequent recent use of oral or systemic glucocorticoid
 - ⇒ history of falls
 - ⇒ family history of hip fracture
 - ⇒ other causes of secondary osteoporosis
 - ⇒ low body mass index (BMI) (< 18.5 kg/m)
 - ⇒ smoking
 - ⇒ alcohol (> 14 units/week for women and > 21 units/week for men).

Methods of risk assessment: NICE recommend using a clinical prediction tool such as FRAX or Q Fracture to assess a patient's 10-year risk of developing a fracture.

- FRAX
 - ⇒ Estimates the 10-year risk of fragility fracture in patients with clinical risk factors (CRFs)
 - ⇒ valid for patients aged 40-90 years (> 90 already considered at high risk.)
 - ⇒ based on international data so use not limited to UK patients
 - ⇒ assesses the 11 factors: age, sex, weight, height, previous fracture, parental fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol intake.
 - ⇒ NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result
 - ⇒ Interpreting the results of FRAX

•	If the FRAX assessment was done without a bone mineral density (BMD)
	measurement
	low risk: reassure and give lifestyle advice
	intermediate risk: offer BMD test
	ligh risk: offer bone protection treatment
•	If the FRAX assessment was done with a bone mineral density (BMD)
	measurement:
	☐ low risk: Reassure
	intermediate risk: consider treatment
	ligh risk: strongly recommend treatment



Q Fracture

- ⇒ estimates the 10-year risk of fragility fracture
- ⇒ developed in 2009 based on UK primary care dataset
- ⇒ can be used for patients aged 30-99 years (this is stated on the Q Fracture website, but other sources give a figure of 30-85 years)
- ⇒ includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants

⇒ Interpreting the results of FRAX

Patients are not automatically categorised into low, intermediate or high risk.
 Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture. This data then needs to be interpreted alongside either local or national guidelines, considering certain factors such as the patient's age.

DEXA scan

- ⇒ NICE recommend against routinely measure BMD (i.e. a DEXA scan) to assess fracture risk without prior assessment using FRAX (without a BMD value) or Q Fracture
- ⇒ There are some situations where NICE recommend arranging DEXA scan directly to assess BMD rather than using one of the clinical prediction tools:
 - before starting treatments that may have a rapid adverse effect on bone density (e.g., sex hormone deprivation for treatment for breast or prostate cancer).
 - in people aged < 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for ≥ 3 months).

When should we reassess a patient's risk (i.e. repeat the FRAX/Q Fracture)?

- if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, or
- when there has been a change in the person's risk factors

Osteoporosis: management

Indications

- History of fragility fractures in postmenopausal women
 - ⇒ Age < 75 years + osteoporotic fragility fractures + confirmed osteoporosis (a T-score of 2.5 SD or below)
 </p>
 - ⇒ Age ≥ 75 years + osteoporotic fragility fractures (a DEXA scan may not be required)
- T-scores ≤ -2.5
- T-score between -1 and -2.5 with severely increased risk of fracture

Bisphosphonates: e.g., alendronate, risedronate

- · The drug of choice for osteoporosis
- Agents
 - ⇒ Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium)
 - recommended only if the 10- year probability of osteoporotic fragility fracture is at least 1%.
 - ⇒ Intravenous bisphosphonates (ibandronic acid and zoledronic acid)
 - recommended only if the 10- year probability of osteoporotic fragility fracture
 is at least 10% OR 1% + difficulty of taking oral bisphosphonates or these
 drugs are contraindicated or not tolerated.
- Mechanism of action: inhibition of osteoclasts → bone resorption (reduce the risk of both vertebral and non-vertebral fractures)
- First-line: alendronate
 - ⇒ around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems.
- Second line (if alendronate not tolerated): risedronate or etidronate
- Instructions for administration
 - ⇒ Should be taken after an overnight fast and at least 30 minutes before the first food or drink (other than water) of the day or any other oral medicinal products or supplementation (including calcium).
 - ⇒ With plenty of water (e.g. 200 ml of water)
 - ⇒ Patients should not lie down for 30 minutes after taking the tablet.
- Side effects
 - ⇒ Hypocalcemia
 - ⇒ Esophagitis, esophageal cancer
 - ⇒ Osteonecrosis of the jaw: most common with intravenous zoledronic acid
- Contraindicated in patients with a GFR less than 35 ml/min
- Treatment review should be performed after 3 to 5 years
 - Continuation of bisphosphonate treatment beyond 3-5 years can generally be recommended in: individuals age ≥75 years, those with a history of hip or vertebral fracture, those who sustain a fracture while on treatment, and those taking oral glucocorticoids.
- Treatment failure
 - ⇒ NICE defines an <u>unsatisfactory response to treatment</u> when a patient has <u>another</u> <u>fragility fracture</u> despite adhering fully to <u>treatment for longer than 1 year</u> and there is evidence of a <u>decline in BMD</u>.

Bisphosphonates should be taken at least 30 minutes before meals, with plenty of water, and the patient should maintain an upright position for at least 30 minutes following intake to prevent esophagitis.

Denosumab

Action

Human monoclonal antibody that inhibits RANK ligand on the surface of osteoclast precursors, which in turn inhibits the maturation of osteoclasts leads to reduced bone reabsorption.

Indication

- ⇒ High risk of fracture + unable to take bisphosphonate (intolerance or a contraindication)
- ⇒ Indicated in patients with impaired renal function or in whom bisphosphonates therapy failed

Administration

⇒ given as a single subcutaneous injection every 6 months. therefore, tolerated by patients who don't want a daily subcutaneous injection

Side effects

- ⇒ Like bisphosphonates it is associated with osteonecrosis of the jaw, but not other adverse events such as reflux oesophagitis.
- ⇒ The risk of a dynamic bone disease may be less for denosumab versus bisphosphonates because it does not accumulate in bone.

Teriparatide: parathyroid hormone analog

Mechanism of action:

- ⇒ Increased osteoblast activity (the main effect) → increased bone growth
- ⇒ increased calcium absorption from the gut and reduced calcium excretion from the kidney.

Indication:

- ⇒ Severe osteoporosis (T-score ≤ -3.5) or for patients + unable to take bisphosphonate (intolerance, contraindication or unsatisfactory response)
 - age ≥ 65 years + T-score of ≤ -4.0 SD, or
 - age ≥ 65 years + T-score of ≤ -3.5 SD + more than two fractures, or
 - age 55–64 years + T-score of ≤ –4 SD + more than two fractures.

Advantages

- ⇒ Effective at reducing vertebral and non-vertebral fractures in post-menopausal women
- ⇒ reduces both pain and disability due to spinal fractures. It is the most appropriate choice to control both the immediate symptoms and for long-term prevention.

Administration

- ⇒ administered once daily by subcutaneous injection and therefore, not preferred by many patients, who don't like injectables.
- ⇒ the maximum total duration of treatment restricted to 18 months.

Side effects

- ⇒ Hypercalcemia (usually transitory)
- ⇒ Increased risk of osteosarcoma in patients with:
 - Paget disease of the bone (or an unexplained elevation of alkaline phosphatase)
 - Prior cancers or radiation therapy

Contraindications

- ⇒ pre-existing hypercalcaemia,
- ⇒ severe renal impairment, (eGFR < 30 mL/minute/ 1.73 m²)
- ⇒ severe hepatic impairment,
- metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of bone)
- ⇒ unexplained elevations of alkaline phosphatase
- previous radiation treatment to the skeleton.

Raloxifene - selective oestrogen receptor modulator (SERM)

Action

⇒ act as a weak oestrogen-receptor agonists in some systems and as oestrogen antagonists in others.

Indication

- Secondary prevention of osteoporotic fragility fractures in postmenopausal women + contraindications to bisphosphonates or those who also require breast cancer prophylaxis.
- ⇒ In patients with breast cancer it should not be used for osteoporosis treatment or prevention until treatment of the breast cancer, including adjuvant treatment, has been completed.
- ⇒ Raloxifene is not recommended for the primary prevention of osteoporotic fragility fractures in postmenopausal women (NICE updated February 2018)

Advantage

- ⇒ increase bone density in the spine and proximal femur
- ⇒ may decrease risk of breast cancer

Disadvantages

- ⇒ reduce risk of vertebral fractures, <u>but has not yet been shown to reduce the risk of</u>
 non-vertebral fractures
- ⇒ <u>less effective</u> in preventing loss of bone mineral density versus bisphosphonates or denosumab.
- ⇒ may worsen menopausal symptoms
- ⇒ increased risk of thromboembolic events

Contraindications

- ⇒ history of venous thromboembolism (VTE)
- ⇒ hepatic impairment, cholestasis
- ⇒ severe renal impairment
- ⇒ unexplained uterine bleeding or endometrial cancer

Strontium ranelate

Action

⇒ 'Dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts

Indication

- ⇒ Severe osteoporosis in men and postmenopausal women at increased risk of fractures [when other treatments are contra-indicated or not tolerated]
- ⇒ the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis due to increased risk of
- ⇒ cardiovascular and thromboembolic events.

Administration

- ⇒ The dose is 2 g once daily in water, preferably at bedtime.
- Advice to avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.

Contraindications

- ⇒ Cerebrovascular disease
- ⇒ Current or previous venous thromboembolic event
- ⇒ Ischaemic heart disease
- ⇒ Peripheral arterial disease
- ⇒ Temporary or permanent immobilisation
- ⇒ Uncontrolled hypertension.
- ⇒ Severe renal impairment
- Should be discontinued during treatment with oral tetracycline or quinolone antibiotics.

Vitamin D and calcium supplementation

- <u>Vitamin D and calcium supplementation</u> should be offered to all women unless the clinician is confident, adequate calcium intake and are vitamin D replete
 - ⇒ 1500 mg/day of calcium and 400-800 pg /day of vitamin D
 - ⇒ Dietary intake of calcium should be:
 - 800-1000 mg/day in childhood through early adulthood
 - 1000-1200 mg/day in the middle years
 - 1500 mg/day in the elderly

(SCE. Sample questions. Mrcpuk.org):

A **78-year-old** woman k/c/o osteoporosis presented with **acute** mid-**thoracic bone pain**. She had p/h/o right **wrist fracture**. **two previous episodes of vertebral fractures**. **On alendronic** acid and calcium and vitamin D tablets regularly for 3 years. DXA scan of spine (L2–L4): T score –3.8. What is the most appropriate treatment?

→ teriparatide

(SCE. Sample questions. Mrcpuk.org):

What cell type in bone primarily senses strain and microdamage?

- → Osteocyte
 - Osteocytes derive from osteoblasts and have long cytoplasmic extensions, which detect strain in bone.

Pathophysiology of bone diseases:

- Osteoporosis → Decreased bone mass, but mineralization is normal.
- Osteomalacia → Decreased bone mineralization (due to vitamin D deficiency)
- Paget's disease → Disorder of bone remodeling (excessive bone resorption, followed by disorganized bone formation occurs, producing thickened but weak bone.)

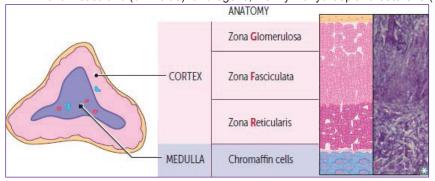
Adrenal gland conditions

Adrenal gland: Basics

Adrenal cortex mnemonic: GFR - ACD

Adrenal cortex (mnemonic GFR - ACD)

- zona Glomerulosa (on outside): mineralocorticoids, mainly Aldosterone
- zona Fasciculata (middle): glucocorticoids, mainly Cortisol
- zona Reticularis (on inside): androgens, mainly Dehydroepiandrosterone (DHEA)



Adrenal medulla

- · The adrenal medulla secretes
 - all the adrenaline in the body
 - ⇒ Small amounts of noradrenaline.
- It essentially represents an enlarged and specialised sympathetic ganglion

Noradrenaline metabolism

- The action of noradrenaline released at sympathetic nerve endings is terminated by which mechanism?
 - The majority are re-uptaked by the axonal terminals → into the neurosecretory granules
 - ⇒ Small amount is metabolised by monoamine oxidase (MAO)
 - Smaller quantities that escape into the circulation are metabolised by catechol-O-methyl transferase (COMT)

Premature adrenarche

Definition and pathophysiology

Premature maturation of the adrenal zona reticularis (adrenarche) → ↑androgen levels → onset of pubarche before age 8 years in girls and age 9 years in boys.

Associated conditions

 Associated with obesity, insulin resistance, and later development of PCOS and/or metabolic syndrome

Epidemiology

- . Most common cause of precocious pubarche
- ♀>♂

Features

- Precocious pubarche: onset of pubic and/or axillary hair growth < 8 years in girls and < 9
 years in boys
- · Adult-type body odor
- Seborrhea, acne
- Increased height for age with a linear growth rate
- Other secondary sexual characteristics are absent (No breast development or testicular enlargement, or frank virilization.)

Diagnosis

- ↑ Serum androgen concentrations (DHEA-S, testosterone)
- Advanced bone age

Differential diagnosis

- · Idiopathic premature pubarche
 - ⇒ Premature onset of pubarche most likely due to increased sensitivity of the pilosebaceous units to normal levels of androgen
 - ⇒ No biochemical evidence of adrenarche (i.e., normal serum androgen concentrations)

Treatment

No treatment is needed besides reassurance.

Premature puberty: signs of secondary sexual development occurring before the age of eight years in girls and the age of nine years in boys are considered premature and warrant careful evaluation.

Dehydroepiandrosterone sulphates (DHEAS)

Overview

- The most abundant circulating adrenal steroid.
- Hormone class: Androgen
- Production site: Zona reticularis of the adrenal cortex
- Function: Substrate in estrogen and testosterone synthesis: DHEA → converted to
 estrogen and testosterone in peripheral tissue. Most of the DHEA is converted to
 androstenedione.
- Regulation of secretion: CRH → ↑ secretion of ACTH in the pituitary gland → ↑ secretion of androgens in the adrenal cortex
- · Decline with age

Clinical significance

- DHEAS is secreted exclusively by the adrenal glands and is therefore a good marker for adrenal androgen production.
- A mildly elevated DHEAS level is common in women with PCOS. In contrast, DHEAS values above 700 ng/dL (7µg/ml, 18umol/L) are suggestive of adrenal neoplasm.
- Loss of functioning adrenal tissue as in Addison's disease may result in symptoms secondary to androgen deficiency, such as loss of libido.
- A trial of dehydroepiandrosterone (DHEA) is recommended in women with primary adrenal insufficiency who have low libido, low energy levels, or depressive symptoms despite glucocorticoid and mineralocorticoid replacement → increasing a sense of wellbeing

May 2008 exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? Dehydroepiandrosterone (DHEA) deficiency

Cortisol

Overview

- Hormone class: Glucocorticoids
- Production site: Zona fasciculata of the adrenal cortex
- Regulation of secretion: CRH → ↑ secretion of ACTH in the pituitary gland → ↑ secretion of glucocorticoids in the adrenal cortex
- Plasma cortisol levels in normal individuals show a circadian rhythm.
- Levels are highest in the early morning and fall to their lowest levels during sleep at around midnight.
- At what time of day is a random cortisol test most likely to be abnormal?
 - ⇒ 2400 hours

Function

- Metabolism: Cortisol plays an important role in the mobilization of energy reserves.
 - ⇒ ↑ Gluconeogenesis to maintain blood glucose levels
 - ⇒ ↑ Glycogen synthesis to maintain glucose storage
 - ⇒ ↑ Protein catabolism
 - ↑ Lipolysis
 - ↑ Appetite
 - ↑ Insulin resistance
- **Immune system:** anti-inflammatory and immunosuppressive effects (see "Pharmacodynamics of glucocorticoids")
- Wound healing: fibroblast inhibition → ↓ collagen synthesis → ↓ wound healing
- Blood pressure: mild mineralocorticoid effect (stimulation of aldosterone receptors in high concentrations) and ↑ potassium excretion → ↑ blood pressure

To remember the effects of cortisol, think "A BIG FIB": increased Appetite, Blood pressure, Insulin resistance, Glucose production, and decreased Fibroblasts, Immunity, and Bone formation.

Cortisol levels are increased in:

- pregnancy
- conditions of physical and emotional stress
- oestrogens
- · oral contraceptives

- amphetamines
- cortisone
- · spironolactone.

What is the immediate precursor in the production of cortisol?

11-Deoxycortisol

No need to evaluate cortisol secretion in critically ill patients

- In a critically ill patient CRH, ACTH and cortisol levels increase rapidly as a haemostatic response to the illness.
- acute illness →↓cortisol binding globulin and albumin →↑free cortisol levels (not truly reflective of adrenal hypersecretion)

Aldosterone

Overview

- Hormone class: Aldosterone is the major circulating mineralocorticoid
- Production site: zona glomerulosa of the adrenal cortex.

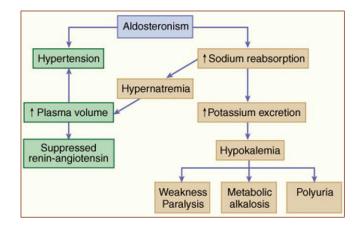
Action

 ↑ Na+ reabsorption → water reabsorption and K+ secretion into the urine → ↑ blood pressure, hypokalemia, and ↑ pH level.

Site of action: principal site: distal renal tubule

Regulation of synthesis and secretion:

- Stimulators
 - ⇒ Hypovolemia →↓ renal perfusion (e.g., due to hypotension, stimulation of β1 receptors in the kidney) → triggers renin release → promotes the conversion of angiotensinogen (produced in the liver) to angiotensin I (AT I), AT I is turned into angiotensin II via angiotensin-converting enzyme (highest concentration in the lungs where it is produced by vascular endothelial cells). Angiotensin II causes vasoconstriction and triggers the secretion of aldosterone.
 - ⇒ Hyperkalemia
- Inhibitors
 - ⇒ Principle inhibitors
 - Hypervolemia
 - Hypokalemia
 - ⇒ Negative feedback: ↑ systemic arterial blood pressure → ANP release from atrial myocytes → inhibition of renin release → vasodilation, natriuresis, and ↑ diuresis



Adrenal hyperandrogenism

Causes

Primary adrenal diseases

- Premature adrenarche
- Adrenal tumors (adenomas, carcinomas, bilateral macronodular adrenal hyperplasia)

ACTH hypersecretion

- Congenital adrenal hyperplasia (CAH)
- ACTH-dependent Cushing's syndrome
- Glucocorticoid resistance
- Cortisone reductase deficiency

Hyperprolactinemia

Exogenous

Androgens

Features

- Virilization: the appearance of male secondary sexual characteristics in a female individual
- Hirsutism: excessive male pattern hair growth (e.g., chin, upper lip, mid-sternum, abdomen, back, buttocks)
- Male-pattern hair loss
- Acne
- · Increased muscle mass
- Voice deepening
- Clitoromegaly
- Rapid onset of virilization is suggestive of exogenous androgen intake or androgensecreting tumors

Differential diagnosis of hyperandrogenism in females

Diagnosis	Characteristic finding
PCOS: Most common (75–80%	Polycystic ovaries on pelvic
of cases)	ultrasound
Nonclassic CAH	↑ 17-Hydroxyprogesterone
Congenital adrenal hyperplasia	Ambiguous genitalia
Cushing disease	↑ 24-hour urine free cortisol
Hypothyroidism	↑ TSH
Androgen-secreting tumor	↑ DHEA-S (> 700 μg/ dL)
(e.g., Sertoli-Leydig cell tumor,	
adrenal)	

Hyperaldosteronism: Overview

Definition: Increased secretion of aldosterone from adrenal gland.

Features and complications

- Hypertension
 - ↑ Aldosterone → ↑ open Na+ channels in the cortical collecting ducts of the kidneys
 → ↑ Na+ reabsorption and retention → water retention → hypertension
- ↓or normal K+
 - ⇒ may be normal in up to 50% of cases
 - ⇒ Diabetes insipidus: hypokalaemia → desensitization of renal tubules to antidiuretic hormone (ADH) → polyuria and polydipsia
- Metabolic alkalosis
 - ⇒ ↑ H+ secretion in the kidney in order to enable ↑ K+ reabsorption
- ↑Aldosterone → reduce nitric oxide bioavailability → ↓ endothelium-dependent vasodilatation → ↑risk of cardiovascular events.
- ↑Aldosterone → ↑ collagen synthesis → promotes myocardial fibrosis and cardiac remodeling →↑myocardial stiffness and ↑ left ventricular mass → ↑risk of ventricular arrhythmias and sudden cardiac death.
- 1° hyperaldosteronism does not directly cause edema due to aldosterone escape mechanism. However, certain 2° causes of hyperaldosteronism (eg, heart failure) impair the aldosterone escape mechanism, leading to worsening of edema.

Aldosterone escape

- Inappropriately elevated aldosterone → sodium and water retention → volume expansion
 → secretion of atrial natriuretic peptide (ANP) and pressure natriuresis → compensatory
 diuresis → "escape" from edema formation and hypernatremia
- In edematous disorders the aldosterone escape mechanism is impaired, resulting in worsening edema.

General causes of hyperaldosteronism

- 1. Primary hyperaldosteronism
 - ⇒ Due to <u>bilateral adrenal hyperplasia</u> (most commonly) and adrenal adenoma (Conn's syndrome) (less commonly)
 - \Rightarrow \uparrow aldosterone $\rightarrow \downarrow$ renin $\rightarrow \uparrow$ aldosterone to renin ratio (ARR).

2. Secondary hyperaldosteronism

- ⇒ Due to renovascular hypertension, fibromuscular dysplasia, juxtaglomerular cell tumors (renin- producing), and oedema (eg, cirrhosis, heart failure, nephrotic syndrome).
- ⇒ The raised aldosterone level is driven by raised renin levels.
- ⇒ ↓blood flow to the kidneys (e.g. due to renal artery stenosis, heart failure, and cirrhosis). → ↓renal perfusion → ↑renin → ↑aldosterone (aldosterone to renin ratio (ARR) will be normal).

Primary hyperaldosteronism

Bilateral idiopathic adrenal hyperplasia is the most common cause of primary hyperaldosteronism

Prevalence: 10–30% of all forms of hypertension Causes

- 1. The most common → Bilateral idiopathic adrenal hyperplasia (70%).
- **2.** Common \rightarrow adrenal adenoma, termed Conn's syndrome.
- 3. Rare → Adrenal carcinoma
- Glucocorticoid deficiency also called glucocorticoid-remediable aldosteronism → high ACTH levels → increased aldosterone production.

Features

- Hypertension: May present with untreated or resistant hypertension
- Hypokalaemia, may leads to:
 - ⇒ fatigue, muscle weakness, cramping, headaches, and palpitations.
 - ⇒ polydipsia and polyuria from hypokalemia-induced nephrogenic diabetes insipidus.
 - ⇒ Abdominal distention (ileus from hypokalemia)
 - ⇒ seen in only 10-40% of patients
- Patient with adrenal adenoma do not have features of hyperandrogenaemia like hirsutism
 as benign adrenal tumours produce cortisol but not the androgens. <u>Absence of hirsutism</u>
 and virilisation in a patient with other features of Cushing's syndrome favours
 adrenal adenoma but needs further investigations.
- Electrolytes: Low/normal potassium. Normal/high sodium
- ABG: Metabolic alkalosis
 - ⇒ Aldosterone act on renal distal convoluted tubule → enhancing sodium reabsorption and potassium and hydrogen ion excretion → Metabolic alkalosis

Screening

- Indications of primary aldosterone screening (using aldosterone / renin ratio after controlling for factors (including medicines) that may confound results):
 - 1. sustained HTN (>150/100 in 3 separate measurements taken on different days;
 - 2. HTN resistant to 3 antihypertensive drugs;
 - **3.** HTN controlled with ≥ **4** medications;
 - 4. HTN + low potassium
 - 5. HTN + adrenal incidentaloma;
 - **6.** HTN + sleep apnea;
 - 7. HTN + family history of early-onset hypertension or stroke before age 40;
 - **8.** HTN + first-degree relatives of patients with primary aldosteronism.

Investigations

- Screening test: Aldosterone-to-renin ratio (ARR)
 - ⇒ ↑aldosterone and ↓renin (aldosterone-to-renin ratios are typically ≥ 20).
 - ⇒ used to screen for primary hyperaldosteronism and differentiate it from other causes of elevated aldosterone (e.g., secondary hyperaldosteronism).
- Confirmatory testing if ARR screening test is positive to verify that aldosterone
 production is nonsuppressible (i.e., not regulated by the RAAS).
 - ⇒ Oral sodium loading test

- Ensure high sodium intake for 3 days and collect 24-hour urine aldosterone on the last day.
- Primary hyperaldosteronism is highly likely if urinary aldosterone > 12 mcg/day.

⇒ Saline infusion test

- Draw baseline laboratory studies (e.g., PRA, Plasma aldosterone), infuse normal saline over 4 hours, and draw laboratory studies again.
- Primary hyperaldosteronism is very probable in patients with aldosterone levels > 10 ng/dL.

⇒ Interpretation

- Aldosterone suppression after interventions: primary hyperaldosteronism unlikely. Consider other diagnoses.
- No aldosterone suppression after interventions: primary hyperaldosteronism confirmed
- Determine the underlying cause (after confirmatory tests)

⇒ Adrenal CT

- Recommended as initial imaging modality after confirmatory tests (preferred over MRI)
- excludes large tumors and helps differentiate possible surgical candidates (e.g., unilateral adenoma) from nonsurgical candidates (e.g., bilateral adrenal hyperplasia).

⇒ Adrenal venous sampling (AVS)

- AVS is the gold standard for biochemically differentiating unilateral aldosterone overproduction from bilateral aldosterone overproduction.
- **Indications:** Both of the following criteria must be met.
 - Adrenal CT suggestive of unilateral hyperaldosteronism
 - Surgical intervention is desired and feasible
- Procedure: catheterization of both adrenal veins and a peripheral vein (e.g., IVC) under fluoroscopy followed by a measurement of the aldosterone-tocortisol ratio of each vein

Findings

- Unilateral disease: significant difference in the aldosterone-to-cortisol ratio between the right and left adrenal veins
- Bilateral disease: little to no difference in ratios between the two adrenal gland veins

⇒ Genetic testing

- for familial hyperaldosteronism type 1 (FH-I) (glucocorticoid remediable aldosteronism [GRA])
 - In patients < 20 years</p>
 - in patients with a family history of PA or stroke at a young age (<40 years),</p>
- In very young patients, we suggest testing for germline mutations in KCNJ5 causing familial hyperaldosteronism type 3 (FH-III).

Aldosterone-to-renin ratio (ARR): Approach

- Eliminate confounding factors before testing
 - ⇒ Correct hypokalemia (because low potassium suppresses aldosterone secretion)
 - ⇒ Encourage normal salt intake (do not restrict salt intake)
 - ⇒ Discontinue agents known to affect **ARR** and use an alternative agent.
 - Drugs need to be stopped: ACEi, ARB, diuretics, and β-blockers for 2 weeks (wash-out period) and spironolactone for 6 weeks.
 - alternative agent which can be used: Alpha-blockers (e.g. doxazosin), calcium channel blockers (e.g. amlodipine) and Hydralazine

- Although ACEi are associated with false negative test results, in clinical practice the ARR can be assessed without stopping these agents. In fact, ACEi may actually improve the sensitivity of the test.
- Alpha blockers such as doxazosin have the lowest effect on the reninangiotensin system
- The blood sample should be taken <u>in the morning</u> during <u>standing position</u> (i.e. with the patient standing for 2 h)
 - ⇒ Values obtained in the upright position are more sensitive than supine test results.
 - ⇒ aldosterone is usually higher when the patient is erect than when supine (in bilateral hyperplasia)
- · Positive screening tests
 - ⇒ Confirm diagnosis (e.g., oral sodium loading test or saline infusion test)
 - ⇒ Identify subtype and etiology (e.g., via imaging, adrenal venous sampling, and/or genetic testing)
- Negative screening tests
 - Consider repeating screening tests if the likelihood of primary hyperaldosteronism remains high.
 - ⇒ Consider other causes of secondary hypertension.

Agents known to affect renin levels include aldosterone receptor antagonists, ACE inhibitors, and potassium-wasting diuretics. Alternatives include alpha blockers and hydralazine.

The effect of drugs on Aldosterone-to-renin ratio (ARR)

- · Drugs with no effect on ARR
 - ⇒ Alpha-blockers
 - **⇒** Calcium channel blockers
 - ⇒ Hydralazine
- Drugs result in false negative
 - **⇒** ACE inhibitors & ARBs → ↑ renin & ↓ aldosterone
 - ⇒ Diuretics → ↑ both renin & aldosterone
- · Drugs result in false positive
 - **⇒** Beta-blockers & Methyldopa → ↓ renin

Differential diagnosis

- Hypertension is also a feature of Liddle syndrome and steroid 11β-hydroxylase deficiency, but aldosterone concentrations are low.
- Secondary hyperaldosteronism:
 - ⇒ ↑renin→ ↑aldosterone secretion (plasma renin activity is normal or increased).
- Adrenal <u>hyperplasia</u> can be differentiated from adrenal <u>adenoma</u> by measuring aldosterone levels on awakening, and 2-4 hours later while standing:
 - ⇒ In adenoma, aldosterone levels decline on standing 2-4 hours later.
 - ⇒ in hyperplasia, levels increase.

Management

- Adrenal adenoma: surgery
 - ⇒ Surgery is the treatment of choice for Conn's adenoma and leads to resolution of hypertension in around 70% of patients.
 - ⇒ Aldosterone inhibition with spironolactone will bring the greatest additional reduction in blood pressure.
- Bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone

Prognosis

- After removal of the adenoma the blood pressure is normal in 70% of patients at 1 year;
- 50% of patients are still normotensive after 5 years.

Bilateral hyperplasia vs adrenal adenoma

bilateral hyperplasia	adrenal adenoma
idiopathic adrenal hyperplasia (IAH)	Aldosterone-producing adenomas (APAs)
Commonest	common
higher prevalence in African Americans, persons of African origin, and, potentially, other blacks.	have more severe hypertension, hypokalemia, and higher urinary aldosterone than IAH.
4 times more prevalent in men than in women	more common in women than in men, with a female-to-male ratio of 2:1.
peaking in the sixth decade of life	The typical patient with an APA is a woman aged 30-50 years.
renin-angiotensin system (RAS)–mediated increase in aldosterone level occurs with upright posture.	decrease in the aldosterone level with upright posture
Loss of normal circadian rhythm of aldosterone secretion (normally: lowest around midnight, and highest in early morning)	preserved of normal circadian rhythm of aldosterone secretion

aldosterone-producing adrenal *adenomas* are commoner in young women, whereas bilateral adrenal <u>hyperplasia</u> tends to occur later and is commoner in <u>men</u>.

Aldosterone receptor antagonists

Agents: spironolactone, eplerenone

Action

- acts on the distal renal tubules as a competitive antagonist of aldosterone increasing sodium and water excretion and reducing potassium excretion (acts as a potassium-sparing diuretic)
- → K+ enters cells in exchange for H+ → amplifies acidosis
- onset of action: requiring 2 or 3 days for maximum effect

Indications

- Hypertension (especially if hypokalemia is also present)
- Ascites/oedema due to congestive heart failure, nephrotic syndrome, or cirrhosis of the liver (mainly spironolactone)
- Hyperaldosteronism (PCOS)
- Nephrogenic diabetes insipidus (amiloride)
- Hypokalemia
- Hyperandrogenic states, e.g., polycystic ovary syndrome (spironolactone)

Adverse effects

- · General side effects

 - ⇒ Gastrointestinal disturbances (nausea, vomiting, diarrhea)
- Spironolactone-specific side effects: endocrine disturbances
 - ⇒ Men: antiandrogenic effects (e.g., gynecomastia, erectile dysfunction)
 - ⇒ Women: amenorrhea

Adrenal incidentaloma

Definition

 asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease.

Prevalence

occur in up to 10% of the population with imaging

Approach

- determine whether the incidentally discovered adrenal mass is:
 - ⇒ Malignant
 - ⇒ Functioning and associated with excess hormonal secretion.

Differential diagnosis

- Phaeochromocytoma (10–15%).
- Adrenocortical carcinoma (5-12%).
- Adrenal myelolipoma (5–10%).
- Metastasis (2–10%; most prevalent breast, lung, kidney).
- Cortisol-secreting adrenal adenoma causing Cushing's syndrome or subclinical Cushing's syndrome (5%).
- Adrenal cysts (5%).
- Ganglioneuroma (4%).

Investigations

Adrenal mass on CT:

- Low density (Hounsfield Units ≤10) = high fat content = benign
- **High density** (>20 HU) = **suspicious** (phaeochromocytoma/adrenocortical carcinoma/metastasis but also lipid-poor adenoma)

The most important thing to **exclude**, particularly in view of any further intervention, is a **phaeochromocytoma** (**plasma free metanephrines**) as <u>catastrophic consequences can</u> ensue following anaesthesia or surgical intervention.

- Exclude malignancy → Noncontrast CT
 - ⇒ If the mass is homogeneous and **low density** (Hounsfield Units ≤10) (lipid-rich) and smaller than 4cm → benign adrenal mass → no further imaging is required
 - ⇒ Surgery if there is any one of the following
 - Evidence of a syndrome of hormonal excess attributable to the tumour

- _
- Imaging features suggestive of malignancy: Mass diameter >4cm, high density (>20 HU).
- ⇒ If the adrenal mass is <u>indeterminate</u> on noncontrast CT and the results of the <u>hormonal work-up do not indicate significant hormone excess</u>, three options should be considered by a multidisciplinary team:
 - immediate additional imaging with another modality, there is little added benefit of MRI over CT in the examination of the adrenals
 - interval imaging in 6–12months (noncontrast CT)
 - If the lesion enlarges by more than 20% (in addition to at least a 5mm increase in maximum diameter) during this period → surgical resection
 - If the lesion enlarges by less than 20% → additional imaging after 6—12months should be performed.
 - Surgery without further delay.

Exclude functional hormonal secretion

- ⇒ Exclude pheochromocytoma by measurement of plasma-free metanephrines
 (most sensitive and specific screening test) or alternatively urinary fractionated
 metanephrines (less specific)
 - The most important thing to exclude, as catastrophic consequences can occur following anaesthesia or surgical intervention.
- ⇒ Exclude cortisol excess by 1mg overnight dexamethasone suppression test
 - post dexamethasone serum cortisol levels ≤50nmol/L (≤1.8µg/dl) exclude autonomous cortisol secretion
- ⇒ Exclude primary aldosteronism aldosterone/renin ratio

Treatment

- Surgery for functional secreting adenoma or suspicious features on imaging
- Observation and monitoring for asymptomatic, <u>nonfunctioning</u> unilateral <u>adrenal mass</u> and benign features on imaging.

The criteria for **surgical removal** of an adrenal tumour is a diameter of **4cm or more** as the risk of primary carcinoma with such size is of the order of 1 in 30.

Congenital adrenal hyperplasia (CAH)

CAH due to 11-beta hydroxylase deficiency can cause apparent mineralocorticoid excess syndrome (AMES) resulting in hypertension and hypokalemia

Which of the following is the best investigation to monitor a patient with classic salt wasting congenital adrenal hyperplasia (CAH)?

⇒ 17 hydroxyprogesterone (17 OHP) levels.

Overview

- Autosomal recessive disorder
- Associated with HLA B47
- · Affects males and females in equal numbers

 Non-classic congenital adrenal hyperplasia is a cause of hyperandrogenism in up to 1 in 1000 females, particularly those of Hispanic, Yugoslavian or Eastern European Jewish descent

Pathophysiology

- CAH is caused by autosomal recessive defects in enzymes that are responsible for the production of cortisol.
- There are three subtypes of CAH:
 - ⇒ 21β-hydroxylase deficiency (~ 95% of CAH)
 - \Rightarrow 11β-hydroxylase deficiency (~ 5% of CAH)
 - \Rightarrow 17 α -hydroxylase deficiency (rare)
- Low levels of cortisol → lack of negative feedback to the pituitary → increased ACTH →
 adrenal hyperplasia and increased synthesis of adrenal precursor steroids
- Non-classical forms result from milder enzyme dysfunction and therefore manifest later in life (adolescence or adulthood).

Types

- 21-hydroxylase deficiency (90%) most common cause

 - ⇒ ↑ Testosterone → virilisation of female genitalia and precocious puberty in males
 - ⇒ ↓ Aldosterone → salt-losing crises (hyponatremia) and hyperkalemia
 - ⇒ ↓11-deoxycorticosterone
 - ⇒ <u>†17 hydroxy-progesterone</u> (commonly used as a screening test)
- 11-beta hydroxylase deficiency (5%)
 - ⇒ ↑ Testosterone → virilisation of female genitalia and precocious puberty in males

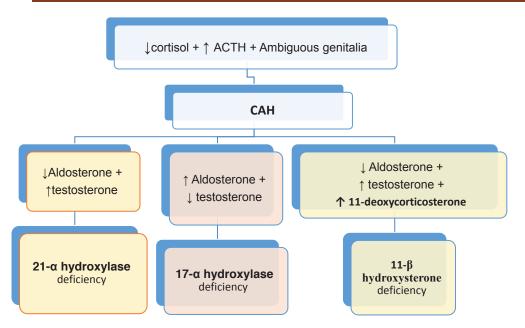
 - ⇒ ↑ 11-deoxycorticosterone, ↑11-Deoxycortisol → Hypertension and hypokalaemia
 - 11 Beta-hydroxylase is responsible for conversion of 11-deoxycorticosterone and 11-deoxycortisol to corticosterone and cortisol. As this enzyme is deficient, levels of these steroids accumulate.
 - 11-deoxycorticosterone has aldosterone-like activity, and in high levels, it causes hypertension and hypokalaemia and inhibits the production of renin and consequently aldosterone.
 - ➡ Mild elevation of 17-OH steroids (not as great as that seen with 21-hydroxylase deficiency), occasionally an incorrect diagnosis of 21-hydroxylase deficiency may however be made.
- 17-hydroxylase deficiency (very rare)
 - ⇒ **17-hydroxylase** converts progesterone to 17-α-hydroxyprogesterone, which subsequently is converted to androstenedione, testosterone, and finally estradiol.
 - \downarrow Estradiol \rightarrow \downarrow menstrual cycle and \downarrow secondary sexual characteristics.
 - Progesterone accumulates and is pushed into the aldosterone synthesis pathway → hypertension and hypokalemia
 - ⇒ ↑ Aldosterone → hypertension and hypokalemia

 - ⇒ ↑ 11-deoxycorticosterone

patients with 11 β -hydroxylase deficiency will present with increased blood pressure, hypokalemia and <u>increased</u> androgen levels, differentiating it from 17 α -hydroxylase deficiency.

A female born with virilisation but has elevated blood pressure likely has a deficiency in 11 beta-hydroxylase.

- 11-deoxycorticosterone decreased only in the 21-hydroxylase deficiency (increased in other 2 types)
- Testosterone decreased only in the 17-hydroxylase deficiency (increased in other 2 types)



Feature

Туре	XX (female) genotype	XY (male) genotype
21β-hydroxylase deficiency	 Hypotension Clitoromegaly and/or male external genitalia along with a uterus and ovaries Precocious puberty Virilization, irregular menstrual cycles, infertility 	Hypotension Normal male external genitalia at birth Precocious puberty
11β-hydroxylase deficiency	Hypertension Clitoromegaly and/or male external genitalia along with a uterus and ovaries Precocious puberty Virilization, irregular menstrual cycles, infertility	Hypertension Normal male external genitalia at birth Precocious puberty
17α-hydroxylase deficiency	Hypertension Normal female external genitalia at birth Delayed puberty (primary amenorrhea) or sexual infantilism	Hypertension Female external genitalia with a blind-ending vagina and intra-abdominal testes at birth Delayed puberty or sexual infantilism

Classical CAH (C-CAH)	Nonclassical CAH (NC-CAH)	
The sever form	 The milder form 	
Less common	more common	
Early onset (during the neonatal period or early infancy)	 Late onset (manifests during late childhood, adolescence, or adulthood) 	
Females present with ambiguous genitalia.	Normal external genitalia	
 Salt-wasting type (~ 67% of all classic forms) → "adrenal crises": vomiting and shock. Non-salt-wasting type (simple virilizing, ~ 33% of all classic forms) → No signs of shock. Males present with precocious puberty at age 2–4. 	Symptoms of hyperandrogenism include hirsutism, acne, menstrual irregularity, androgenic alopecia, and impaired fertility	

- ACTH excess →hyperpigmentation (common feature in all forms of CAH)
- Under- and over-treatment of CAH → Premature epiphyseal closure → short stature
- · Patients might complain of no other symptoms apart from primary amenorrhoea.
- The clinical presentation may be indistinguishable from polycystic ovarian syndrome, with hirsutism being a dominant feature.

Туре	21β-hydroxylase deficiency	11β-hydroxylase deficiency	17α-hydroxylase deficiency
Blood pressure	Hypotension	Hypertension	Hypertension
Acid-base disorders	Metabolic acidosis	Metabolic alkalosis	Metabolic alkalosis
17-Hydroxyprogesterone	Elevated	Elevated	Decreased
11-Deoxycorticosterone	Decreased	Elevated	Elevated
Corticosterone	Decreased	Decreased	Elevated
Potassium	Elevated	Decreased	Decreased

Diagnosis

- Screening is conducted by measuring 17-hydroxyprogesterone → elevated
 - ⇒ can help to distinguish between PCOS and non-classical CAH.
- ACTH stimulation test (synacthen stimulation test)
 - ⇒ can diagnose 21-OH deficiency when the plasma 17-OH progesterone are more than 30 nmol/L.
 - ⇒ In individuals with borderline 17-hydroxyprogesterone levels, we recommend obtaining a complete adrenocortical profile after a cosyntropin stimulation test
- Genotyping
 - ⇒ **only** indicated when:
 - results of the adrenocortical profile after a cosyntropin stimulation test are equivocal, or
 - cosyntropin stimulation cannot be accurately performed (i.e., patient receiving glucocorticoid), or
 - for purposes of genetic counseling.
- Normal ultrasound scan will rules out other causes of primary amenorrhoea (Turner syndrome and testicular feminization).

Management

- · Glucocorticoid replacement
 - ⇒ Hydrocortisone in neonates and children
 - ⇒ Prednisolone or dexamethasone in adolescents and adults
 - ⇒ steroids given in reverse circadian rhythm, i.e. a higher dosage at night and a lower dose in the morning (when steroids are given in higher doses at night → ACTH is suppressed → ↓ over-secretion of adrenal androgens and ↓the normal physiological steroid peak in the morning)
- Symptomatic
 - ⇒ If the main concern is infertility, ovulation induction is the treatment of choice.
 - If hirsutism is the presenting problem, then anti-androgens (such as flutamide) should be used.

Restoring functional anatomy by surgery

- ⇒ minimally virilized girls: surgical options, include <u>delayed surgery</u> and/ or observation until the child is older
- \Rightarrow In severely virilized females (single urogenital opening) \rightarrow <u>early surgery</u> to repair the urogenital sinus

Specific treatment

⇒ 21β-hydroxylase deficiency

- Lifelong fludrocortisone therapy (aldosterone substitution)
- Sodium chloride (salt) supplements, especially during infancy and childhood

⇒ 11β-hydroxylase deficiency

- Spironolactone to block mineralocorticoid receptors
- Reduced dietary sodium intake

⇒ 17α-hydroxylase deficiency

- Spironolactone to block mineralocorticoid receptors
- Estrogen replacement therapy for female genotype; may be started in early puberty
- Reduced dietary sodium intake

⇒ Salt-wasting CAH

- Fluid resuscitation with intravenous normal saline
- Intravenous dextrose in patients with significant hypoglycemia
- Immediate administration of glucocorticoid replacement therapy

⇒ Nonclassic CAH

- Women: combined oral contraceptives are first-line treatment (alternatively glucocorticoid therapy)
- Men: usually no treatment required

Monitoring of treatment

- Efficacy of treatment is best monitored by 17-OH progesterone and androstenedione levels
- Renin activity levels can be used to monitor the adequacy of mineralocorticoid and sodium replacement.

The dose of glucocorticoids must be increased during severe infection, critical illness, and perioperatively to meet increased demands to prevent adrenal crisis.

Glucocorticoid remediable aldosteronism (GRA)

GRA should be suspected as the cause of primary aldosteronism when there is a **positive family history** and the onset of **hypertension is before age 21 years**.

Overview

- GRA is a rare subtype of primary aldosteronism, also called familial hyperaldosteronism (FH) type I
- Autosomal dominant mutation leads to ACTH responsive aldosterone production from the zona fasciculata rather than the zona glomerulosa.
- It occurs because the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene.
- usually associated with bilateral adrenal hyperplasia.

Features

- Strong family history of early resistant hypertension and haemorrhagic strokes is characteristic.
- Elevated plasma aldosterone and suppressed renin
- Hypokalaemia
 - ⇒ potassium is normal in more than one-half of cases of GRA in contrast to the hypokalaemia frequently seen in primary aldosteronism.
- Markedly increased levels of 18-oxocortisol and 18-hydroxycortisol.
- Responsive to corticosteroid therapy.

Complications

 increased risk ruptured intracranial aneurysms → hemorrhagic stroke (higher than that reported in autosomal dominant polycystic kidney disease.)

Diagnosis

- dexamethasone suppression test
- genetic testing (now preferred over dexamethasone suppression testing for making the diagnosis of GRA)

Treatment

 physiologic doses of a glucocorticoid will correct the overproduction of aldosterone by suppressing ACTH.

The main clinical clues suggesting GRA in the normokalaemic, hypertensive patient are:

- 1. family history of hypertension
- 2. onset at a young age
- **3.** frequent development of marked hypokalemia after the administration of a thiazide diuretic (which increases sodium delivery to the aldosterone-sensitive potassium secretory site in the cortical collecting tubule).

The combination of low renin, high aldosterone and raised urinary oxocortisol suggests glucocorticoid remediable aldosteronism (GRA).

GRA is autosomal dominant, and therefore genetic testing is the most appropriate investigation. (SCE-question samples-mrcpuk.org)

Pseudohyperaldosteronism

Definition

• Pseudohyperaldosteronism is characterized by a clinical picture of hyperaldosteronism with suppression of plasma renin activity and aldosterone.

Feature

- Hypertension
- Salt retention
- Hypokalaemia
- Low renin and aldosterone concentrations

Causes

- · Congenital adrenal hyperplasia
- · Exogenous mineralocorticoid
- Cushing syndrome
- Liddle syndrome
- 11β-hydroxysteroid dehydrogenase deficiency
- Glucocorticoid resistance
- Excessive licorice ingestion: Excessive consumption of licorice can lead to inhibition of cortisol degradation → hypertension associated with hypokalemia.

Syndrome of Apparent Mineralocorticoid Excess (SAME)

Definition

• **AME** is a rare form of pseudohyperaldosteronism characterized by very early-onset and severe hypertension, associated with low renin levels and hypoaldosteronism.

Causes

- Congenital deficiency of 11-beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2): Autosomal recessive mutation.
- Acquired reduction of the activity of the (11 bHSD) enzyme caused by:
 - ⇒ carbenoxolone
 - ⇒ grapefruit juice
 - ⇒ ↑ liquorice consumption (glycyrrhizic acid): black substance produced from the root of a plant used in medicine and sweets)

Pathophysiology

- With normal 11- beta-hydroxysteroid dehydrogenase type 2 (11-beta-HSD2) activity: 11-beta-HSD2 converts cortisol into cortisone (cortisone, unlike cortisol, does not activate mineralocorticoid receptors).
- With 11-beta-HSD2 deficiency (or inhibition): ↓ cortisol conversion to cortisone → ↑ cortisol → ↑ mineralocorticoid receptor activity.

Feature

- Hypertension
- Low birth weight
- Failure to thrive
- Muscle weakness
- Polyuria and polydipsia due to nephrogenic diabetes insipidus
- Renal failure
- ↑ Ratio of free urinary cortisol (urinary tetrahydrocortisol) to free urinary cortisone.

 (AME patients create less cortisone)

In Syndrome of Apparent Mineralocorticoid Excess, cortisol has the SAME action as aldosterone.

Differential diagnosis

- differentiate between AME and Liddle's Syndrome by administering a potassium-sparing diuretic:
 - ⇒ Liddle's syndrome: **only** respond to a diuretic that binds the ENaC channel,
 - ⇒ AME: respond to a diuretic that binds to ENaC or mineralcorticoid receptor.

Treatment

- · Cessation of licorice ingestion
- Spironolactone to decrease the mineralocorticoid effects
- Thiazide in hypercalciuria or nephrocalcinosis
- Corticosteroids: exogenous corticoids block ACTH and suppress the endogenous secretion of cortisol.

Spironolactone (an aldosterone receptor antagonist) is effective in treating the syndrome of apparent mineralocorticoid excess but not Liddle syndrome!

Phaeochromocytoma

Phaeochromocytoma: do 24 hr urinary metanephrines, not catecholamines

PHaeochromocytoma - give PHenoxybenzamine before beta-blockers

The 5 P's of pheochromocytoma:

Pressure (BP)

Pain (headache)

Perspiration

Palpitations

Pallor/diaphoresis

Pheochromocytoma rule of 10's:

10% extra-adrenal

10% bilateral

10% malignant

10% occur in children

10% familial

Pheochromocytoma = Episodic hypertension

Pheochromocytoma is part of MEN II.

Definition

 Phaeochromocytoma is a rare tumors arising from <u>chromaffin cells</u> of the adrenal medulla and secreting catecholamines. Chromaffin cells are modified post-ganglionic sympathetic cells that release catecholamines after stimulation by pre-ganglionic sympathetics.

Overview

- The majority of pheochromocytomas are benign, unilateral, catecholamine-producing tumors.
- Tumors arise from chromaffin cells, which are derived from the neural crest.
- Present in up to 1% of all hypertensive patients
- The peak incidence is between ages 20 to 40.
- Equal sex distribution
- familial in 10%
- bilateral in 10%
- malignant in 10%
- Localisation
 - ⇒ ~ 90% adrenal medulla (physiologically activated by acetylcholine)
 - $\Rightarrow \sim$ 10% extra-adrenal in the sympathetic ganglia (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)
 - ⇒ ~ 10% at multiple locations
- 25% of pheochromocytomas are hereditary (germline mutations):
 - ⇒ Multiple endocrine neoplasia type 2 (MEN 2A, MEN 2B)
 - ⇒ Neurofibromatosis type 1 (NF1)
 - ⇒ Von Hippel-Lindau disease (VHL)

Features

- **Episodic hypertension** (around 90% of cases, may be sustained)
 - □ Triggers for paroxysmal elevations in blood pressure: foods and beverages high in tyramine (e.g., red wine, aged cheese), surgery, pressure on the tumor (e.g., during massage), or certain drugs (e.g., beta blockers, MAOIs)
- Paroxysmal
 - ⇒ Throbbing headache (80%) the most common presenting feature
 - ⇒ Diaphoresis (60%)
 - ⇒ Palpitations, tachycardia (70%)
 - ⇒ Pallor
 - ⇒ Abdominal pain and nausea
 - ⇒ Anxietv
- Weight loss due to increased basal metabolism
- Hyperglycemia
- Signs of polycythemia, if EPO is secreted
- Other features consistent with associated familial disorders:
 - ⇒ MEN 2A: medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia
 - ➡ MEN 2B: medullary thyroid cancer, pheochromocytoma, oral/intestinal neuromas, and marfanoid habitus
 - ⇒ NF1: cutaneous neurofibromas, cafe-au-lait spots, and Lisch nodules
 - \Rightarrow VHL: renal cell carcinoma, hemangioblastoma, angiomatosis, and

pheochromocytoma

5 most important Problems (5 P's) of Pheochromocytoma: increased blood Pressure, head Pain (headache), Perspiration, Palpitations, and Pallor

Hypertensive crises can be triggered by palpation of the tumor on abdominal exam.

Investigations

- Plasma free metanephrines test
 - ⇒ The best initial test
 - ⇒ The most <u>sensitive</u> test
- · 24 hr urinary collection of metanephrines
 - □ The most specific test (sensitivity 86%)
 - ⇒ False positive urinary metanephrines can occur as a result of:
 - hypoglycaemia, stress, exercise, drugs such as methyldopa, dopamine agonists or ganglion-blocking antihypertensives, various foodstuffs including coffee, chocolate, bananas and citrus fruits.
 - ⇒ The presence of **noradrenaline alone** usually indicates an **extra-adrenal tumour**.
 - <u>Paragangliomas</u> (exception—organ of Zuckerkandl) <u>secrete noradrenaline</u> <u>only</u>, as they lack **PNMT**. Phenylethanolamine-N-methyltransferase (**PNMT**) is necessary for methylation of noradrenaline to adrenaline and is cortisol-dependent.
 - ⇒ <u>Small adrenal tumours</u> tend to <u>produce more adrenaline</u> whereas <u>larger adrenal</u> <u>tumours produce</u> <u>more noradrenaline</u>
 - ⇒ <u>Tricyclic antidepressants</u> and <u>labetalol</u> interfere with adrenaline measurements and should be **stopped for 4 days**
 - ⇒ Plasma and urinary methoxytyramine levels are indicators of malignancy and can show isolated increases in patients with 'biochemically negative' malignant
- Clonidine suppression tests
 - ⇒ may be used to differentiate patients who have borderline catecholamine levels
 - Clonidine 300 micrograms orally—failure of suppression of plasma catecholamines into the normal range at 120 and 180min is suggestive of a tumour
- Genetic testing: if MEN2A, MEN2B, NF1, or VHL is suspected
- Immunohistochemical staining: positive for chromogranin, synaptophysin, and NSE
- Adrenal/abdominal CT or MRI (after positive biochemistry tests to localize tumor)
 - ⇒ The definitive methods for localisation
 - ➡ MRI: unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI.
- Meta-iodo-benzyl guanidine (MIBG) scanning
 - demonstrates specific uptake in sites of sympathetic activity
 - ⇒ used in cases where a tumour is confirmed biochemically but cannot be identified on CT or MRI.
 - ⇒ Performed preoperatively to exclude multiple tumours.
 - ⇒ Phenoxybenzamine may lead to false –ve MIBG imaging, so these scans should be performed before commencing this drug where possible.
- 18F fluorodopamine PET scanning is superior to MIBG in localizing metastatic disease.



The image reveals a large left suprarenal mass. The appearances are typical of a which, unlike most other adrenal tumours, demonstrates a distinctive 'bright white' signal on T2-weighted MRI.

Management

- **Initial management** →The patient must be first <u>stabilized with medical management</u>:
 - ⇒ Alpha-blocker (e.g. phenoxybenzamine), should be given first, before a betablocker
 - ⇒ beta-blocker (e.g. propranolol): Unopposed beta blockade should not be used in the management of phaeochromocytoma because of the risk of paradoxical increases in blood pressure
- Laparoscopic tumor resection (adrenalectomy): treatment of choice
 - ⇒ No-touch technique
 - ⇒ Open surgical resection is reserved for large or invasive tumors.
 - ⇒ Preoperative blood pressure management: combined alpha-adrenergic and beta-adrenergic blockade
 - First, a non-selective irreversible alpha-blocker is given: Phenoxybenzamine blocks alpha-1 and alpha-2 adrenoceptors equally and irreversibly
 - After sufficient alpha-adrenergic blockade, a beta-blocker may be started for additional blood pressure control and control of tachyarrhythmias.

Prognosis

- benign phaeochromocytoma →The 5-year survival rate is 95%
- malignant phaeochromocytoma → The 5-year survival rate is 40%
- Hypertension may persist in 25% patients who have undergone successful tumour removal.
- SHB gene mutation patients are associated with a shorter survival.

Primary hypoadrenalism (Addison's disease)

Addison's disease is associated with metabolic acidosis

Primary hypoadrenalism is diagnosed by a short synacthen test and a failure to increase cortisol levels to above 500nmol/L

Pathophysiology

- Damage to the adrenal gland leads to the deficiency in all three hormones produced by the adrenal cortex: androgen, cortisol, and aldosterone. Clinical findings are noted after 90% of the adrenal cortex has been destroyed.
- Hypoaldosteronism → hypotension (hypotonic hyponatremia and volume contraction), hyperkalemia, metabolic acidosis
- Hypoandrogenism → Loss of libido + Impaired spermatogenesis (in men)
- Hypocortisolism leads to:
 - ⇒ ↑ ACTH → ↑ production of POMC (in order to increase ACTH production) → ↑
 melanocyte-stimulating hormone (MSH) → hyperpigmentation of the skin (bronze skin)
 - ⇒ ↑ ADH level → retention of free water → dilutional hyponatremia
 - ⇒ ↓ Expression of enzymes involved in gluconeogenesis → ↓ rate of gluconeogenesis → hypoglycemia
 - ⇒ Lack of potentiation of catecholamines action → hypotension

Prevalence

- Prevalence is around 5 per 100,000.
- There is a female: male preponderance of 2:1

Causes

- Autoimmune destruction of the adrenal glands
 - the commonest cause of hypoadrenalism in developed countries (80% of cases)
 - ⇒ 70% of patients have circulating anti-adrenal antibodies.
- Associated with other autoimmune conditions such as
 - ⇒ pernicious anaemia
 - ⇒ thyroid disease
 - ⇒ Type 1 diabetes
 - ⇒ Vitiligo
 - Chronic active hepatitis.
- Infectious (e.g. mycobacterial, fungal, HIV)
 - ⇒ Adrenal tuberculosis (15% of cases)
 - the most common cause in developing countries.
 - In case with high ESR, TB adrenalitis should be considered
 - the best investigation → CT abdomen
 - reversible with anti-tuberculosis medications if given at an early
 - ⇒ HIV: affect10% of patients with HIV, due to cytomegalovirus (CMV)
 - ⇒ Fungal: Histoplasmosis: A systemic fungal infection caused by Histoplasma
 - ⇒ Acute meningococcal sepsis due to Neisseria meningitidis → disseminated intravascular coagulation (DIC) → acute adrenal hemorrhage, also known as Waterhouse-Friderichsen syndrome.
 - Neisseria meningitidis is a gram-negative diplococcus that grows on chocolate agar.
 - purpuric rash classically appears on the trunk and extremities secondary to the DIC
- Infiltration of the adrenal glands
 - ⇒ Tumors (adrenocortical tumors, lymphomas, metastatic carcinoma)
 - ⇒ Amyloidosis
 - ⇒ Hemochromatosis
- Vascular (eg, hemorrhage, emboli, thrombus)

- ⇒ Anti-phospholipid syndrome (Hughes' syndrome) → haemorrhage through adrenal vein thrombosis → adrenal infarction
- ⇒ Anticoagulant overdose → bilateral hemorrhage in the adrenal glands → acute adrenal insufficiency. Flank pain, hypotension refractory to resuscitative efforts, and hypoglycemia indicate acute adrenal insufficiency due to heparin overdose.
- ⇒ Traumatic, iatrogenic (eg, surgery)
- Drugs-induced adrenal insufficiency → Cortisol synthesis inhibitors
 - ⇒ Antifungals: Ketoconazole, Fluconazole
 - ⇒ Antibiotics: Rifampin
 - ⇒ Antiepileptics: Phenytoin, Barbiturates

Thinning of pubic and axillary hair is seen in females with Addison's disease due to reduced production of testosterones from the adrenal gland

Most cases of adrenal insufficiency are subclinical and only become apparent during periods of stress (e.g., surgery, trauma, infections), when the cortisol requirement is higher!

Features

Hormonal changes	Clinical features	Laboratory findings
Hypoaldosteronism	HypotensionSalt craving	HyponatremiaHyperkalemiaNormal anion gap metabolic acidosis
Hypocortisolism	 Gastrointestinal complaints (e.g., nausea, vomiting, diarrhea) Weight loss, anorexia Fatigue, lethargy, depression Muscle aches Weakness Sugar cravings Orthostatic hypotension 	 Hypoglycaemia Hyponatremia
Hypoandrogenism	Loss of libidoLoss of axillary and pubic hair	↓ DHEA-S
Elevated ACTH	 Hyperpigmentation of areas that are not normally exposed to sunlight (e.g., palmar creases, mucous membrane of the oral cavity) pathognomonic 	↑ Melanocyte stimulating hormone (MSH))





This patient has buccal pigmentation which raises the possibility of adrenal insufficiency

Investigations

short Synacthen test is definitive diagnostic test

- Routine laboratory studies
 - ⇒ AGB → Normal anion gap metabolic acidosis due to ↓ bicarbonate
 - ⇒ CBC → normocytic normochromic anaemia, eosinophilia, lymphocytosis
 - \Rightarrow Electrolytes \rightarrow Na \downarrow , K \uparrow , Ca \uparrow
 - ⇒ Blood glucose → Hypoglycemia
- Endocrine studies: Use stepwise endocrine testing
 - ⇒ Morning cortisol level: initial test
 - the diagnosis can be ruled out by a basal serum cortisol value in the upper end of the reference range or higher
 - cortisol > 500 nmol/l makes Addison's very unlikely
 - < 100 nmol/l strongly suggest hypocortisolism.</p>
 - 100-500 nmol/l should prompt ACTH stimulation test to be performed
 - Random cortisol levels are of limited value, as cortisol secretion varies diurnally and with physiological stress.
 - Cortisol levels are influenced by cortisol-binding globulin (CBG) and albumin levels.
 - ⇒ Morning ACTH level: obtain if morning cortisol is low
 - Primary adrenal insufficiency: elevated ACTH levels > 100 pg/mL
 - Secondary/tertiary adrenal insufficiency: ACTH levels low to normal
 - ACTH secretion is subject to diurnal variation, which is why a morning sample is desirable.
 - Exogenous glucocorticoids (via any route) can suppress ACTH secretion through negative feedback.
 - ⇒ Standard-dose ACTH stimulation test (short Synacthen test, cosyntropin test): gold standard test to confirm the diagnosis of primary adrenal insufficiency
 - Method
 - Administration of 250 mcg exogenous ACTH to stimulate cortisol secretion
 - Measurement of cortisol levels before and 30 and 60 minutes after injection
 - Physiological response: exogenous ACTH → ↑ cortisol
 - If a patient is on prednisone, prednisolone, or dexamethasone, temporarily switch them to hydrocortisone and hold hydrocortisone 24 hours prior to testing.
 - Interpretation
 - In primary adrenal insufficiency: peak cortisol level < 18–20 μg/dL (< 500–550 nmol/L): no rise in cortisol level</p>
 - In secondary/tertiary adrenal insufficiency: usually a rise in cortisol > 18–20 μg/dL (> 500–550 nmol/L)
 - Variant: low-dose (1 mcg) ACTH stimulation test
 - Uses a smaller dose of exogenous ACTH and is thought to better mimic physiological conditions
 - Studies show mixed results regarding its superiority to the standard-dose test.

- Adrenal autoantibodies: anti-21-hydroxylase: present in approximately 80% of cases.
- Imaging
 - ⇒ CXR: Screen for tuberculosis if an infective cause is suspected.
 - ⇒ CT or MRI adrenal glands: Screen for adrenal hemorrhage and malignant or infiltrative disease.

Primary hypoadrenalism

- hyperprolactinaemia is reported and is glucocorticoid-responsive.
- High plasma renin and angiotensin II.
- High ACTH
- High lipotropin
- **High** plasma vasopressin

Management

- Replacement therapy:
 - ⇒ Glucocorticoid → oral hydrocortisone.
 - Usually given in 2 or 3 divided doses. Patients typically require 20-30 mg per day, with the majority given in the morning dose
 - Medications and food interacting with hydrocortisone and cortisone acetate:
 - Drugs that affect hydrocortisone metabolism: need to increase the dose:
 - Anti-epilepsy/barbiturates, Antituberculosis
 - Drugs that affect hydrocortisone metabolism: need to decrease the dose:
 - Grapefruit juice, Liquorice
 - ⇒ Mineralocorticoid → fludrocortisone
 - Drugs that affect fludrocortisone (need to be avoided): Diuretics, Acetozolamide, Carbenoxolone, liquorice, NSAIDS
 - Drugs that affect fludrocortisone (need to increase the dose): Drospirenonecontaining contraceptive
 - Essential hypertension in a patient with PAI should be treated by adding a <u>vasodilator</u>, not by stopping the mineralocorticoid replacement, although a dose reduction should be considered.

Patient education

- □ During travelling
 - Patient's with Addison's should be given a <u>hydrocortisone injection kit</u> when travelling to use it if unable to take oral hydrocortisone or vomiting. This can prevent Addisonian crisis
- ⇒ During an intercurrent illness
 - the glucocorticoid dose should be doubled
 - If unable to take the normal oral hydrocortisone then the patient should be advised to take IM hydrocortisone to avoid adrenal crisis. This is why all patients with Addison's disease should have IM hydrocortisone for these situations.
- ⇒ During shift work
 - Patients who work night-time shifts will need to adjust their dose schedule according to the work pattern (e.g. 10 mg upon awakening before going to work, instead of taking the first dose at 07:00 h).doses should be taken from when waking
 - Glucocorticoid therapy should ideally mimic endogenous cortisol rhythm with the lowest level at time of falling asleep and highest at waking.

- When a patient shifts their daytime routine, such as working on night shifts or travelling, the patient should be advised to take their morning dose on waking and maintain the timing from there.
- ⇒ During an event of increased activity:
 - If significantly strenuous activity (e.g. marathon)
 - double the dose of glucocorticoid and mineralocorticoids
 - Mineralocorticoid therapy will be eventually required in adrenal insufficiency to counter intravascular volume depletion. It is important in the presence of increased fluid loss that the mineralocorticoid dose is adjusted. This is why doubling of the dose is advised.
 - If the patient was just on hydrocortisone then no additional fludrocortisone would be needed.
 - If less strenuous activity (such as a long hike, was planned)
 - increasing the dose of hydrocortisone by 5-10mg would be reasonable, without any change in fludrocortisone. This change would also apply for any day that increased activity is planned for.
- **□** During pregnancy
 - The doses of neither of the medications (hydrocortisone and fludrocortisone) should be preemptively increased in the first trimester.
- A trial of dehydroepiandrosterone (DHEA) is recommended in women with primary adrenal insufficiency who have <u>low libido</u>, <u>low energy</u> levels, or <u>depressive</u> symptoms despite glucocorticoid and mineralocorticoid replacement.

Waterhouse-Frederickson syndrome

 adrenal failure due to bleeding into the adrenal glands (otherwise referred to as haemorrhagic adrenalitis) and is most commonly caused by meningococcal septicaemia.

A person with Addisons' who vomits should take IM hydrocortisone until

May 2008 exam: Addison's disease C/O a decrease in her libido. On examination there is a slight loss of pubic hair. What is the most likely cause? Dehydroepiandrosterone (DHEA) deficiency

Wolman's syndrome is characterised by:

- 1. primary adrenal failure.
- 2. hepatosplenomegaly, and
- 3. steatorrhoea.

Addisonian crisis

Signs/symptoms of Addisonian crisis

Neurological	Haemodynamic	Biochemical
syncopeconfusionlethargyconvulsions	hypotensionhypothermia	hyponatraemiahyperkalaemiahypoglycaemia

Management of Addisonian crisis (medical emergency)

- Intravenous fluids
 - ⇒ 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- I.V Corticosteroids
 - □ In a patient without a previous diagnosis of adrenal insufficiency → IV
 □ dexamethasone, as this will not interfere with cortisol assays needed for a short synacthen test, unlike hydrocortisone.
 - ⇒ For patients with a previously known diagnosis of adrenal insufficiency → 100 mg IV hydrocortisone because diagnostic testing is not necessary. continue hydrocortisone 6 hourly until the patient is stable.
 - ⇒ Mineralocorticoid (fludrocortisone) administration is not necessary in the acute setting because high cortisol exerts weak mineralocorticoid action.

Secondary hypoadrenalism

long Synacthen test can be used to distinguish primary adrenal failure from secondary adrenal failure

Definition

Adrenal hypofunction due to a lack of adrenocorticotropic hormone (ACTH)

Pathophysiology

- ↓ ACTH → hypoandrogenism and hypocortisolism
- Aldosterone synthesis is not affected (mineralocorticoid production is controlled by RAAS and angiotensin II, not by ACTH).
- If ↓ ACTH induced by ↓ CRH, then it is called tertiary adrenal insufficiency (↓ CRH → ↓ ACTH).

Causes

- **Hypopituitarism**: ↓ ACTH → ↓ endogenous cortisol
 - ⇒ Pituitary tumors
 - ⇒ Craniopharyngioma (in youngers)
 - ⇒ Irradiation
- Conditions that decrease CRH production (tertiary adrenal insufficiency): ↓ CRH → ↓
 ACTH → ↓ cortisol release
 - ⇒ The most common cause is sudden discontinuation of chronic glucocorticoid therapy (e.g., infection, trauma, surgery) during prolonged glucocorticoid therapy
 - ⇒ Rarer causes include hypothalamic dysfunction (e.g., due to trauma, mass, haemorrhage, or anorexia).

Secondary and tertiary adrenal insufficiency are far more common than primary adrenal insufficiency

Feature

- Symptoms and signs are similar to those of Addison disease
- Differentiating features include:
 - Absence of hyperpigmentation because ACTH secretion is not increased.
 - ⇒ Absence of mineralocorticoid deficiency (Aldosterone synthesis is not affected)
 - No dehydration or hypotension

- Relatively normal electrolyte. Hyponatremia if it occurs, is due to increased vasopressin secretion → volume expansion → dilutional hyponatremia. Hyperkalemia is not present
- Associated features of underlying cause, e.g. visual field defects if pituitary tumour.
- ⇒ Other endocrine deficiencies may manifest due to panhypopituitarism (↓thyroid and gonadal function and hypoglycemia). Adrenal crisis is likely if a patient is treated with thyroxine, without hydrocortisone replacement.
- ⇒ **Hypoglycemia is more common** in secondary adrenal insufficiency.

Primary adrenal insufficiency \rightarrow Pigments the skin. Secondary adrenal insufficiency \rightarrow Spares the skin. Tertiary adrenal insufficiency is due to \rightarrow Treatment (cortisol).

Diagnosis

Confirmatory Serum Testing for Secondary Adrenal Insufficiency		
Test	Result	
ACTH	Low (< 5 pg/mL)	
Cortisol	Low (< 5 μg/dL [138 nmol/L])	
ACTH stimulation test (short Synacthen test)	Normal or subnormal	
Prolonged (24-h) ACTH stimulation test (Long Synacthen test)	Cortisol should continue to rise for 24 h	

- Long Synacthen test (prolonged ACTH stimulation test for 24 h)
 - ⇒ Aim:
 - To diagnose secondary (or tertiary, ie, hypothalamic) adrenal insufficiency.
 - ⇒ Before the test:
 - The simple short test is usually done initially, because a normal response obviates the need for further investigation.
 - If short Synacthen test is subnormal (failure to respond to ACTH →↓ cortisol)
 and secondary adrenal insufficiency is suspected → do long Synacthen test
 - Because pituitary failure may cause adrenal atrophy and hence failure to respond to ACTH, the patient may need to be primed with long-acting ACTH 1 mg IM once/day for 3 days before the ACTH stimulation test if pituitary disease is suspected.
 - ⇒ Method:
 - Cosyntropin 1 mg IM is given, and cortisol is measured at intervals for 24 h, typically at 1, 6, 12, and 24 h.
 - **⇒** Interpretation:
 - In primary adrenal failure: No significant cortisol rise.
 - In secondary adrenal failure: gradually rises cortisol to a peak at 24 hours
 - ❖ Prolonged stimulation of the adrenal glands by ACTH in the long Synacthen test → gradually rises cortisol to a peak at 24 hours → confirm the diagnosis of secondary adrenal failure.
 - in some cases of long-standing adrenal atrophy due to secondary adrenal insufficiency, the adrenal glands will not respond even after 24 hours and will require several daily doses of depot Synacthen before an adrenal response is seen.
- CT or MRI of the brain to rule out a pituitary tumor or pituitary atrophy.

Corticosteroids

Patients on long-term steroids should have their doses doubled during intercurrent illness

Mechanism of action

Corticosteroids are hydrophobic small molecules and thus freely pass through cell
membranes. They bind to inactive cytosolic glucocorticoid receptors, which then translocate
to the nucleus to act as nuclear transcription regulators.

Summary of effects of systemic corticosteroids

 The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

Minimal glucocorticoid activity, very high mineralocorticoid activity	activity, high	Predominant glucocorticoid activity, low mineralocorticoid activity	Very high glucocorticoid activity, minimal mineralocorticoid activity
Fludrocortisone	Hydrocortisone	Prednisolone	Dexamethasone Betmethasone

Side-effects

- · Glucocorticoid side-effects
 - ⇒ endocrine:
 - impaired glucose regulation,
 - increased appetite/weight gain,
 - hirsutism.
 - hyperlipidaemia
 - Cushing's syndrome: moon face, buffalo hump, striae
 - ⇒ musculoskeletal:
 - osteoporosis,
 - proximal myopathy,
 - avascular necrosis of the femoral head
 - ⇒ immunosuppression:
 - increased susceptibility to severe infection.
 - reactivation of tuberculosis
 - ⇒ psychiatric: insomnia, mania, depression, psychosis
 - ⇒ gastrointestinal: peptic ulceration, acute pancreatitis
 - ⇒ ophthalmic: glaucoma, cataracts
 - ⇒ suppression of growth in children
 - ⇒ intracranial hypertension
- Mineralocorticoid side-effects
 - ⇒ fluid retention
 - ⇒ hypertension

The pathogenesis of corticosteroid induced osteoporosis is multifactorial:

 Corticosteroids reduce osteoblastic activity, and the resulting osteoblast/osteoclast imbalance causes loss of bone. Corticosteroids reduce intestinal calcium absorption and lower circulating sex steroid levels

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
 - $\,\Rightarrow\,$ For milder concurrent illnesses oral prednisolone is usually doubled for a few days.
 - ⇒ For sever illness convert prednisolone temporarily to IV glucocorticoids, conventionally 50-100 mg of hydrocortisone six hourly.
 - ➡ Mineralocorticoid dose is always left unchanged.
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have: received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses
- Low dose i.v hydrocortisone → improve outcome in sepsis
 - ⇒ More recent randomised controlled trials have suggested that there is a benefit in sepsis when lower physiological doses of steroids are given.
- Lactose-containing methylprednisolone preparations should not be used in patients with cows' milk allergy
- Corticosteroids are recognised to inhibit osteoblast activity and increase osteoblast apoptosis. This is thought to be a more important component in bone loss with respect to steroid induced osteoporosis versus any effect on osteoclasts.
- Whilst corticosteroids do increase osteoclast activity, it is thought to be their effect on osteoblast activity which has a greater impact on bone mineral density.

Steroid induced hypogonadism

- Body builders may be involved in the illicit use of anabolic and androgenic steroids. These
 results are consistent with ongoing use of androgens.
- The hypogonadism, if persistent, may be treated with human chorionic gonadotropin.

Relative potencies of the glucocorticoids

- It is important to know the relative potencies of the glucocorticoids.
- 1 mg prednisolone is equivalent to 4 mg of hydrocortisone
- Dexamethasone for instance is roughly 30 times more potent than hydrocortisone.

Steroid doses equivalence

- 1mg prednisolone = 4mg hydrocortisone
- 1mg dexamethasone = 7mg prednisolone
- Dexamethasone is roughly 30 times more potent than hydrocortisone.

Anabolic steroids

- Anabolic steroids can be taken orally (eg stanozolol) or may have to be injected because of their high first-pass metabolism (eg testosterone enantate)
- Among their many unwanted effects, they increase the risk of cardiovascular disease:
 - blood pressure is elevated
 - blood lipid profiles change, with increased LDL-cholesterol and decreased HDL-cholesterol
 - haematocrit is increased, leading to a prothrombotic tendency, although there is a protective decrease in plasma fibrinogen concentrations with prolonged use

Abuse of androgenic steroids

- The abuse of androgenic steroids amongst people who practise certain sports is quite common.
- side effects
 - ⇒ Paranoid delusions
 - **⇒** aggressive behaviour.
 - ⇒ Other side effects of these illicit drugs include:

- ⇒ Acne
- ⇒ Gynaecomastia (also increase in breast cancer risk)
- ⇒ Hypertension
- ⇒ Hypercholesterolaemia, and
- ⇒ Hepatic tumours.

Cushing's syndrome (Hypercortisolism)

Cushing's syndrome - hypokalaemic metabolic alkalosis

Small cell lung cancer accounts 50-75% of cases of ectopic ACTH

The <u>overnight</u> dexamethasone suppression test is the <u>best</u> test to diagnosis Cushing's syndrome

Pathological definition

- Cushing's syndrome →hypercortisolism from any cause.
- Cushing's disease → hypercortisolism caused by ACTH-secreting pituitary adenoma → the most common cause of Cushing's syndrome (75% of cases).

Epidemiology

- Commoner in \mathcal{L} (\mathcal{L} :3, 3–15:1).
- Age: most commonly, 20-40 years

Causes

- Exogenous (iatrogenic) Cushing syndrome
 - ⇒ Prolonged glucocorticoid therapy → hypercortisolism → decreased ACTH → bilateral adrenal atrophy
 - ⇒ Most common cause of hypercortisolism
 - ⇒ Dexamethasone poses a higher risk for development of iatrogenic Cushing disease. Shorter-acting agents, such as prednisone or hydrocortisone, are recommended alternatives.
- Endogenous Cushing syndrome
 - ⇒ Primary hypercortisolism (ACTH-independent Cushing syndrome) (5–10%)
 - Autonomous overproduction of cortisol by the adrenal gland → ACTH suppression → atrophy of the contralateral adrenal gland
 - Adrenal adenomas
 - Adrenal carcinoma: abnormal liver function tests (LFTs) suggest metastases.
 - Adrenal hyperplasia
 - ⇒ Secondary hypercortisolism (ACTH-dependent Cushing syndrome)
 - Pituitary ACTH production (Cushing disease) (~ 75%): Pituitary adenomas
 → ACTH secretion → bilateral adrenal gland hyperplasia
 - Ectopic ACTH production (~ 15%): Paraneoplastic syndrome (e.g. small cell lung cancer) → ↑ ACTH secretion → bilateral adrenal gland hyperplasia

- characteristically associated with very low potassium levels.
- $\ensuremath{\mathscr{F}}$ weight loss suggests there is an underlying malignancy \rightarrow ectopic ACTH

Pseudo-Cushing's (Alcohol-induced Cushing's syndrome)

- Obese alcoholic consumer → ↑CRH secretion or impaired hepatic metabolism of cortisol→ cushingoid appearance → Induce false positive dexamethasone suppression test or 24 hr urinary free cortisol
- Investigations
 - ➡ Midnight serum cortisol: The most appropriate next step in the investigation of alcoholic patient after confirming hypercortisolism
 - The hallmark of true Cushing's syndrome is lack of diurnal variation in serum cortisol. However, in pseudo-Cushing's diurnal variation is normally maintained.
 - ⇒ Insulin stress test (insulin tolerance test)
 - used to differentiate between true Cushing's and pseudo-Cushing's
 - in pseudo-Cushing's the insulin tolerance test will demonstrate hypoglycaemia with a rise in ACTH and cortisol.
 - In Cushing's syndrome, this hypoglycaemia induced response is lost.
 - contraindicated in epilepsy, ischaemic heart disease, or hypoadrenalism.
 - ⇒ Raised MCV may point to alcoholism
- Management: promote weight loss, and strict control of alcohol intake. Usually mild and disappears rapidly during abstinence from alcohol.

Features

- Skin
 - ⇒ Thin, easily **bruising** with ecchymoses
 - Cortisol breaks down proteins in bone and skin, so the free amino acids can be used to make sugar. This leads to bruising, striae, muscle wasting, and osteoporosis.
 - ⇒ Stretch marks (classically purple abdominal striae)
 - ⇒ Hirsutism, Acne: due to increased adrenal androgen levels
 - ⇒ Delayed wound healing
 - ⇒ Flushing of the face
 - ⇒ If secondary hypercortisolism: often hyperpigmentation (darkening of the skin due to an overproduction of melanin), especially in areas that are not normally exposed to the sun (e.g., palm creases, oral cavity)
 - Caused by excessive ACTH production because melanocyte-stimulating hormone (MSH) is cleaved from the same precursor as ACTH called proopiomelanocortin (POMC)
 - Not a feature of primary hypercortisolism
- Neuropsychological: lethargy, depression, sleep disturbance, psychosis
- Musculoskeletal
 - ⇒ Osteopenia, osteoporosis → pathological fractures, avascular necrosis of the femoral head, vertebral collapse
 - ⇒ Muscle atrophy/weakness (proximal myopathy)

Endocrine and metabolic

- ⇒ Insulin resistance → hyperglycemia (see "Diabetes mellitus") → mild polyuria in the case of severe hyperglycemia
- ⇒ Dyslipidemia
- ⇒ Fat redistribution: "moon face," buffalo hump, truncal obesity, thin arms and legs
- ⇒ \triangle : Decreased libido
- ⇒ ⊊: Decreased libido, virilization, and/or irregular menstrual cycles (e.g., amenorrhea)

· Other features

- ⇒ Secondary hypertension (~ 90% of cases): due to fluid and sodium retention
- ⇒ Increased susceptibility to infections (due to immunosuppression)
- ⇒ Peptic ulcer disease
- ⇒ Cataracts
 - Most commonly → Posterior subcapsular cataract
 - The predominant feature of a posterior subcapsular cataract is glare when looking into bright lights, either from the sun or car headlights.
- ⇒ Menstrual irregularity is found in 84% of female patients with Cushing syndrome

General laboratory findings

- ⇒ Hyperglycemia (Diabetes mellitus may occur in 30%): Cortisol → ↑gluconeogenesis (from protein break down → free amino acids) →↑glucose levels
- ⇒ Hyperlipidemia
- ⇒ Hypokalaemic
- ⇒ Metabolic alkalosis: caused by increased urinary loss of H+ (acid)
- ⇒ Leukocytosis
- ⇒ Low oestradiol

Diagnosis: confirm Cushing's syndrome (hypercortisolism) and then localise the lesion.

- Tests to confirm Cushing's syndrome (hypercortisolism): the two commonly used are:
 - 1. Overnight low dose (1 mg) dexamethasone suppression test (ODST)
 - Sensitivity and specificity are 98% (most sensitive)
 - Low sensitivity and specificity in obese subjects (75-80%) therefor (UFC) will be best than (ODST) in obese
 - If cortisol is suppressed → Cushing's disease is the likely cause.
 - If cortisol is not suppressed → either primary adrenal Cushing's syndrome (low/undetectable ACTH) or ectopic ACTH is the cause (high ACTH).
 - Causes of false-positive ODST (meaning that a diagnosis of Cushing is suggested incorrectly)
 - cytochrome p450 inducers (Dexamethasone is metabolised by the cytochrome p450 system, specifically by the CYP3A4 isoenzyme).
 - ↑oestrogen exposure (eg, pregnancy, oral contraceptives)
 →↑corticosteroid-binding globulin (CBG): need 6 weeks washout before the test
 - If ODST is not offered in a question, then 24 hour urinary free cortisol is the next best answer

2. 24 hr urinary free cortisol (UFC)

⇒ Can be useful for outpatient screening

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- ⇒ Due to false –ve rate of 10% it should not be used alone. should be followed by an overnight dexamethasone suppression test. If both of these tests are normal, then Cushing syndrome could be ruled out.
- ⇒ Factors lead to false +ves: Fenofibrate, carbamazepine, and digoxin.
- Tests to localise the lesion (source of the hypercortisolism):
 - 1) The first step is to measure ACTH level:
 - ACTH level low: This means the origin is in the adrenal gland → Scan the gland with a CT or MRI.
 - ACTH level high: This means the origin is either in the pituitary gland or from the ectopic production of ACTH.
 - 2) The next step is a high-dose (8 mg) dexamethasone suppression test (to differentiate between Cushing disease and ectopic ACTH production)
 - If high-dose dexamethasone suppresses the ACTH → adequate suppression of cortisol levels to less than 50% of baseline: the origin is the **pituitary**. Scan the pituitary.
 - If high-dose dexamethasone does not suppress the ACTH (No cortisol suppression): the origin is an ectopic production of ACTH or a cancer that is making ACTH. Scan the chest for lung cancer or carcinoid.
 - Serum cortisol levels would remain unchanged with both low-level and high-level dexamethasone testing due to the lack of glucocorticoid receptors to facilitate negative feedback on the ectopic cells producing the ACTH. Anterior pituitary corticotrophs do have these receptors and, therefore, will be suppressed by any dose of dexamethasone.
 - The use of high-dose dexamethasone suppression testing is an area of debate, owing to its variable sensitivity and specificity.

3) CRH stimulation test

- ACTH and cortisol levels increase further: Cushing disease
- No increase in ACTH or cortisol levels: ectopic ACTH production

4) Inferior Petrosal sinus sampling (IPSS)

- IPSS is the only test with sufficient diagnostic accuracy to differentiate Cushing's disease from ectopic ACTH production (the test of choice)
- Patient with high ACTH without definitive lesions on MRI should undergo IPSS: Up to 40% of patients with Cushing's disease will not have visible lesions on pituitary/sellar MRI. (The overall sensitivity of MRI to diagnose Cushing disease is only 60% to 70%.)
- It samples venous blood draining from the pituitary gland, using a femoral approach. A raised ACTH from here compared to the periphery suggests a pituitary cause.
- Patients with an IPSS central/peripheral gradient of ACTH >2:1 or 3:1 after corticotrophin-releasing hormone (CRH) stimulation → Cushing's disease
- Patients without high central/peripheral gradient of ACTH → ectopic ACTH →
 do CT of the chest, abdomen, and pelvis to look for a tumour secreting ACTH.
 - The most common tumours that secrete ACTH are bronchial or thymic carcinoids.

Dexamethasone suppression tests

- The low-dose (1 mg) dexamethasone suppression test: used to confirm Cushing's syndrome (hypercortisolism)
- The high-dose (8 mg) dexamethasone suppression test: used to differentiate between
 Cushing disease and ectopic ACTH production.

If a 24-hour urine free cortisol is elevated (one evidence of hypercortisolism), and there is an inadequate suppression on 1 mg overnight dexamethasone test (confirmatory test for hypercortisolism) in a patient suspected of Cushing syndrome, the next step would be to measure ACTH (to localise the lesion)

The following table summarizes the characteristics of the 3 sources of Cushing disease.

	Pituitary Tumor	Ectopic ACTH Production	Adrenal Adenoma
ACTH	High	High	Low
High-dose	Suppression	No suppression	No suppression
dexamethasone			
Specific test	MRI, Petrosal vein sampling	Scan chest and abdomen	Scan adrenals
Treatment		Removal	

Which techniques is the best in differentiating between ectopic Cushing's syndrome and pituitary dependent Cushing's disease?

- ⇒ Inferior petrosal sinus sampling
- ⇒ The high-dose dexamethasone suppression test can differentiate between the two forms of Cushing's syndrome, but is not as accurate as inferior petrosal sinus sampling.

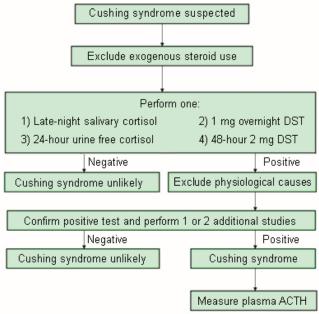
Which feature would favour benign adrenal adenoma as the cause of Cushing's syndrome over the other causes?

⇔ Absence of hirsutism and virilisation (adrenal adenoma produces cortisol but not the androgens)

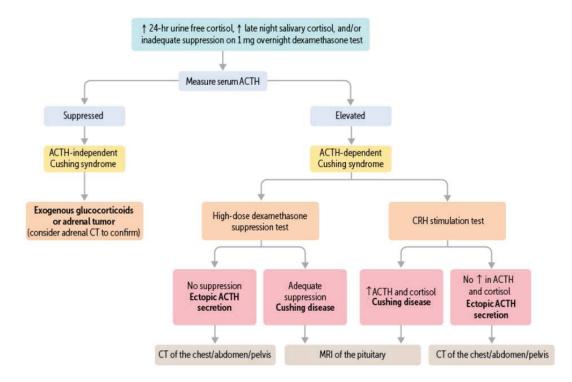
Diagnostic steps in suspected Cushing's syndrome

- Step 1 : Exclude exogenous corticosteroid use
- Step 2: Screen for hypercortisolism with 1 of the 4 high-sensitivity tests
 - 1) late-night salivary cortisol;
 - 2) 1 mg overnight low-dose dexamethasone suppression testing,
 - 3) 24-hour urinary free cortisol; or
 - 4) 48-hour 2 mg dexamethasone suppression testing.
- **Step 3:** Exclude physiological causes of hypercortisolism (from history)
 - physical stress, malnutrition, alcoholism, depression, pregnancy, class III obesity (BMI 40 or above) or metabolic syndrome.
- Step 4: If an initial screening test is positive, and physiological causes of hypercortisolism have been excluded: confirm hypercortisolism with at least 1 additional test of the 4 highsensitivity tests.
- Step 5: Once endogenous hypercortisolism is confirmed, plasma ACTH should be measured.
 - \Rightarrow If ACTH is suppressed, diagnostic testing should focus on the adrenal glands. \rightarrow adrenal CT \rightarrow adenoma.
 - ⇒ If ACTH is not suppressed, pituitary or ectopic disease should be sought.

Algorithm for the diagnosis of Cushing syndrome



In the diagnosis of hypercortisolism, hormone analysis always precedes imaging because microadenomas of the pituitary do not always appear upon imaging. Furthermore, imaging can reveal inactive adrenal tumors (incidentalomas) and pituitary tumors in many healthy individuals.



Treatment

- Fit for surgery
 - ⇒ Pituitary adenoma →Trans-sphenoidal hypophysectomy/adenomectomy is the initial treatment of choice.
 - ⇒ Adrenocortical tumor: laparoscopic or open adrenalectomy
 - ⇒ Laparoscopic adrenalectomy would be advised where pituitary surgery has failed.
 - ⇒ The recurrence rate for Cushing's disease after surgery is 20-30% and depends on the size of the tumour with macroadenomas having a higher rate of relapse.
 - ⇒ ACTH-secreting ectopic tumor: resection of the ectopic foci (e.g., bronchial carcinoid)
- · Unfit for surgery
 - ⇒ Ketoconazole may be an effective treatment for patients unfit for surgery
 - ➡ Mitotane is an adrenolytic drug licensed for symptomatic treatment of advanced or inoperable adrenocortical carcinoma → improve the prognosis

Which drug is most appropriate to improve metabolic parameters prior to surgery in pituitary-dependent Cushing's?

 \Rightarrow Metyrapone \rightarrow inhibits 11-beta hydroxylase \rightarrow inhibits cortisol production.

What is the optimum time for the administration of hydrocortisone to a patient undergoing bilateral adrenalectomy for Cushing's disease?

⇒ Immediately following the removal of both adrenal glands.

Perioperative management of a cortisol producing adenoma includes:

 Peri and postoperative hydrocortisone with further assessment of postoperative cortisol secretion May 2008 exam: A 62-year-old man is investigated for hypertension and proximal myopathy. On examination he is noted to have abdominal striae. Which one of the following is most associated with ectopic ACTH secretion?

⇒ Small cell lung cancer

Disorder	Investigation of choice
Cushing	Overnight Dexamethasone Test
Cushing- vs. Pseudo-cushing	Insulin Stress Test
Addison	Short Synacthen Test
Pheochromocytoma	24H Urinary metanephrines
Acromegaly	Oral Glucose Tolerance Test

Diabetology

Pancreatic Hormones

- Islet A cells produce glucagon
- Islet beta cells produce:
 - 1. insulin
 - 2. C peptide
 - 3. pro-insulin
 - 4. amylin
 - 5. GABA
- Islet **D** cells produce **somatostatin**
- F cells produce pancreatic polypeptide

Glucose transporters

Glucose entrance to the cells

- To intestinal epithelial cells and proximal renal tubular cells → via Sodium/Glucose cotransporter (SGLT)
- To all other cells of the body → Glucose Transporters (GLUTs).

Sodium/glucose cotransporter (SGLT)

- Glucose uptake into the enterocyte from the lumen of the GI tract occurs primarily via the sodium-dependent **SGLT-1** secondary active transport mechanism.
 - ⇒ SGLT-1 is a transporter found predominantly in the gut, and is responsible for glucose absorption.
 - ⇒ The Na+-glucose cotransporter also transports galactose. Thus, when the cotransporter is congenitally defective, the resulting glucose and galactose malabsorption causes severe diarrhea that can be fatal if glucose and galactose are not removed from the diet.
- Function
 - ⇒ transport glucose actively across lumen against concentration gradient
 - energy provided by transport of sodium down its concentration gradient

- location
 - ⇒ small intestine (SGLT1) → 2:1 Na⁺:Glu
 - ⇒ proximal tubule of nephron (SGLT2) → 1:1 Na⁺:Glu
- Glucose exit from the enterocyte into the extracellular fluid occurs by facilitated diffusion and is mediated by the membrane transporter, **Glut-2**.

Glucose Transporters (GLUTs).

GLUT-1

- function
 - ⇒ basal glucose uptake (GLUT1 and GLUT3 continually transport glucose into cells at an essentially constant rate.)
 - high affinity
 - transporters saturated at normal blood glucose levels
 - ensures glucose entry to cells
- location
 - ⇒ wide distribution in tissues in the body (brain, erythrocytes, endothelial cells, cornea etc.)
 - ⇒ especially expressed in cells with barrier functions, such as Blood- Brain barrier, blood-retinal barrier, blood placental barrier, blood testes barrier
 - ⇒ most importantly it is expressed in erythrocytes.

GLUT-2

- GLuT 2 is a glucose transporter expressed in pancreatic beta cells.
- It is a fundamental part of the glucose sensing apparatus in the pancreatic beta cells and helps trigger insulin release in response to increasing glucose concentrations in the extracellular fluid.
- GluT 2 is also expressed in hepatocytes and may act as a glucose sensor in the portal vein system.
- It may have a role in regulating glucagon secretion and feeding behaviour.
- function
 - ⇒ **low affinity glucose uptake** (high-capacity but a low affinity transporter)
 - in the fasting state glucose does not enter cells
 - mediates glucose surplus storage in liver when blood glucose levels rise
 - facilitates insulin release in β-cells
- location
 - ⇒ hepatocytes
 - ⇒ pancreatic β-cells
 - ⇒ kidney
 - ⇒ small intestines

In healthy individuals, which glucose transporter is required for triggering insulin secretion in response to elevated blood glucose concentration?

⇒ GluT 2

GLUT-3

- function
 - ⇒ high affinity glucose uptake
 - glucose preferentially accessed by neurons in low-glucose states
- location
 - ⇒ brain
 - ⇒ neurons

GLUT-4

- GLUT-4 is the only glucose transporter that is responsive to circulating insulin levels.
 - ⇒ ↑plasma glucose concentration → ↑circulating insulin → ↑expression of GLUT-4 →
 ↑glucose transport into the cell.
 - ⇒ The other types of glucose receptors (GLUT-1,2,3,&5) are not responsive to circulating insulin levels
 - ⇒ exogenous insulin in the treatment of diabetes mellitus results in increased glucose uptake via the GLUT-4 transporter.
 - ⇒ This high-affinity glucose transporter plays a crucial role in avoiding postprandial hyperglycemia, since insulin secreted by the pancreatic beta cells promotes glucose uptake into myocytes.
- function
 - ⇒ insulin-controlled uptake of glucose
 - ⇒ basal level of glucose intake without insulin
 - presence of insulin ↑ translocation of transporters to the cell membrane
 - ↑↑↑ glucose uptake
 - also stimulated by exercise
- location
 - ⇒ adipocytes
 - ⇒ myocytes
 - ⇒ cardiomyocytes

Which glucose transporter is responsible for assisting glucose across the plasma membrane in myocytes?

⇒ GLUT 4

Glut-5

- located on the apical portion of the enterocyte
- function: entry of fructose into the cell.
- GLUT-1 = BBB (Blood- Brain barrier)
- GLUT-3 = "Brain"

Glycaemic index (GI)

Definition

• The glycaemic index (GI) describes the capacity of a food to raise blood glucose compared with glucose in normal glucose-tolerant individuals.

Classification

- Carbohydrates can be scored from 0 to 100 where glucose has a GI of 100.
- High GI index foods have a value of 70 or above, medium 56-69 and low <55.
- Apples, peaches oranges and even chocolate are considered low GI (less than 55).
- through different preparation, the GI can alter <u>mashed</u> potatoes (70) and <u>baked</u> potatoes (85) have a high GI (above 70) whilst boiled potatoes have a moderate GI of 58.
- Foods only appear if they contain carbohydrate hence meats, eggs and fish do not appear in the GI index.
- Generally, the lower the GI index the 'better' the carbohydrate.

Classification	Examples
High GI	White rice (87), baked potato (85), white bread (70)
Medium GI	Couscous (65), boiled new potato (62), digestive biscuit (59), brown rice (58)
Low GI	Fruit and vegetables, peanuts

The risk of foods with a high GI

- may be associated with an increased risk of obesity
- the post-prandial hyperglycaemia associated with such foods may also increase the risk of type 2 diabetes mellitus.

Metabolic syndrome

Features of the metabolic syndrome are:

- · Diabetes or pre-diabetes.
- Hypertension
- Central adiposity
- High triglycerides or low HDL cholesterol

Definition

 the co-occurrence of metabolic risk factors for both type 2 diabetes and cardiovascular disease (CVD) (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension).

Pathophysiology

• the key pathophysiological factor is insulin resistance.

Diagnostic criteria

- WHO criteria (1999): Presence of insulin resistance (type 2 diabetes mellitus, impaired glucose tolerance, or impaired fasting glucose), Plus two of the following:
- 1. blood pressure: > 140/90 mmHg
- 2. dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
- central obesity: waist: hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
- microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin: creatinine ratio > 30 mg/g
- International Diabetes Federation criteria (2005): presence of central obesity (defined
 as waist circumference > 94cm for Europid men and > 80cm for Europid women, but can be
 assumed if BMI >30 kg/m²) Plus two of the following:
 - 1. **Triglycerides**: > 1.7 mmol/L, or specific treatment for this lipid abnormality
 - HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality.
 - 3. BP: > 130/85 mm Hg, or active treatment of hypertension
 - **4. Fasting glucose > 5.6 mmol/L**, or previously diagnosed type 2 DM.

Management

- Aggressive lifestyle modification focused on weight reduction and increased physical activity
- Long-term exercise upregulates expression of GLUT4, which may reduce hyperglycemia in patients with type 2 DM or metabolic syndrome.
- Orlistat (an inhibitor of gastrointestinal lipases) with diet, reduces the risk of diabetes in an obese patients by 38% more than diet alone.

Alström syndrome (AS)

- · rare autosomal recessive disease
- caused by mutations in the ALMS1 gene.
- characterized by multiorgan dysfunction.
- · Key features are:
- childhood obesity, hyperinsulinemia, early-onset type 2 diabetes, and hypertriglyceridemia. Thus, AS shares several features with the common metabolic syndrome, namely obesity,
- · blindness due to congenital retinal dystrophy,
- sensorineural hearing loss.
- dilated cardiomyopathy in over 60% of cases,
- developmental delays in 50 % of cases.

Pre-diabetes or impaired glucose regulation (IGR)

Definition:

- impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. Includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).
- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation (IGR) when talking to other healthcare professionals

Incidence

• Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes.

Impaired fasting glucose (IFG)

- Definition → fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l
 - ⇒ Mechanism → due to hepatic insulin resistance
 - ⇒ people with IFG should then be offered an oral glucose tolerance test (OGTT) to rule out a diagnosis of diabetes.

Impaired glucose tolerance (IGT)

- Definition → fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- Mechanism → due to muscle insulin resistance
- Patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Identification of patients with prediabetes: Who should be assessed for the risk of type 2 diabetes?

- all adults aged 40 and over,
- people of South Asian and Chinese descent aged 25-39,
- adults with conditions that increase the risk of type 2 diabetes:
 - ⇒ cardiovascular disease, stroke, hypertension,
 - ⇒ obesity.
 - ⇒ polycystic ovary syndrome,
 - ⇒ history of gestational diabetes
 - ⇒ mental health problems.

Diagnosis

	normal	Prediabetes	Diabetes mellitus
Fasting glucose	≤ 6 mmol/l	≥ 6.1 – 6.9 mmol/l impaired fasting glucose (IFG)	≥ 7 mmol/l
2h glucose during an OGTT	< 7.8 mmol/l	7.8 -n 11 mmol/l Impaired glucose tolerance (IGT)	≥ 11.1 mmol/l
HA1c	< 42 mmol/mol < 6%	42 – 47 mmol/mol (6.0 – 6.4%)	≥ 6.5%

Complication

- progression to type 2 diabetes mellitus (T2DM)
- The risk of developing type 2 diabetes in patient with (IGT) \rightarrow 60% over 6 years
- † risk of macrovascular disease (e.g. coronary artery disease). No risk of microvascular complications of diabetes such as retinopathy and nephropathy.

Management

The best way to reduce the incidence of type 2 diabetes in individuals with IGT is \rightarrow Intensive lifestyle change

- · Lifestyle modification: weight loss, increased exercise, change in diet
 - ⇒ intensive diet and lifestyle change (that results in loss of approximately 5% of initial body weight) can reduce progression from impaired fasting glucose (or impaired glucose tolerance) to frank type 2 diabetes by approximately 50%.
- NICE recommend metformin for adults at high risk 'whose blood glucose measure (fasting
 plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite
 their participation in an intensive lifestyle-change programme'

Which drug classes is most well known as a cause of impaired glucose tolerance?

⇒ Atypical antipsychotics

Both typical antipsychotics and antihypertensives (thiazides and beta blockers), have been shown in meta-analyses to be associated with impaired glucose tolerance and increased risk of type 2 diabetes.

The risk is relatively larger for risperidone than thiazides & β.blocker

MRCPUK- part- 1-September 2009 exam: The fasting glucose of asymptomatic patient comes back as 6.5 mmol/l. The test is repeated and reported as 6.7 mmol/l. How should these results be interpreted? Impaired fasting glycaemia

Diabetes mellitus: Type 1 overview

Definition

 Type 1 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia due to absolute insulin deficiency.

Epidemiology

- 5% to 10% of all patients with diabetes.
- more common in Europeans and less common in Asians.

Pathophysiology

- Genetic susceptibility and environmental triggers (often associated with previous viral infection) → autoimmune response (CD4 +T-cell mediated) with production of autoantibodies, e.g., anti-glutamic acid decarboxylase antibody (anti-GAD), anti-islet cell cytoplasmic antibody (anti-ICA) → progressive destruction of β cells in the pancreatic islets → absolute insulin deficiency → decreased glucose uptake in the tissues.
- Type 1 diabetes becomes clinically evident upon destruction of approximately 70-80 % of beta cell mass.

Risk factors

- Genetic risks
 - ⇒ **HLA association** (HLA DR4 > HLA DR3)
 - ⇒ The familial risk of Type 1 diabetes:
 - Only 10% of patients have a positive family history
 - If both parents have type 1 DM → ≈ 40% (in offspring)
 - If the father has type 1 DM → 3–6%
 - If the mother has type 1 DM → 2-3%
 - If one identical <u>twin</u> has type 1 DM, the risk in the unaffected twin \rightarrow 30-50%.
 - If a sibling (brother or sister) has type 1 diabetes → 5–6%
- Viral infections
 - Only congenital rubella infection has been <u>definitively</u> linked to an increased risk for type 1 diabetes.
 - ⇒ Studies attempting to link other viruses to type 1 diabetes, including enterovirus and rotavirus, have had mixed results.
 - ⇒ Enteroviruses may play a role in both protection from and susceptibility to type 1 diabetes.
- Presence of autoantibodies → 50% risk of DM over five years.
- Loss of first phase insulin response (postprandial insulin secretion in response to a meal, begins within 2 minutes of nutrient ingestion and continues for 10 to 15 minutes) → indicator of significant impending beta cell destruction → 100% risk of DM over two years.
- · Association with other autoimmune conditions
 - ⇒ Hashimoto thyroiditis
 - ⇒ Type A gastritis
 - ⇒ Celiac disease
 - ⇒ Primary adrenal insufficiency

Which feature is most closely associated with the imminent development of type 1 diabetes? \rightarrow Loss of first phase insulin response

Features

- · Age of onset below 50 years
- Diabetic ketoacidosis (DKA) is the first manifestation in one-third of cases
- BMI below 25 kg/m²
- Rapid weight loss (the cardinal feature of absolute insulin deficiency.)
- Classic symptoms of hyperglycemia (Polyuria, Polydipsia, Polyphagia)
- · Increased susceptibility to infections

Weight loss is an indicator of type 1DM even if the patient is obese \rightarrow insulin is the best treatment (SCE. Questions sample. Mrcpuk.org)

Diagnosis of DM: any one of the following

- Fasting plasma glucose ≥126 mg/dL (7 mmol/L) on at least two occasions
- Symptoms of hyperglycemia and a plasma glucose ≥200 mg/dL (11.1 mmol/L)
- Plasma glucose ≥200 mg/dL (11.1 mmol/L) measured two hours after a standard glucose load in an oral glucose tolerance test
- Glycated hemoglobin (A1C) ≥6.5%.

Investigations for type 1

- C-peptide
 - \Rightarrow \downarrow C-peptide levels indicate an absolute insulin deficiency \rightarrow type 1 diabetes
 - ⇒ ↑ C-peptide levels may indicate insulin resistance and hyperinsulinemia → type
 2diabetes
- Antibodies detected in patients who later go on to develop type 1 DM:
 - ⇒ Glutamic Acid Decarboxylase (GAD) antibody
 - found in 70-90% of type1 diabetics.
 - 10 fold increases the risk of developing IDDM.
 - 10% of adults who have been classified as having type 2 diabetes may have (ICA) or (GAD) antibodies, indicating autoimmune destruction of beta cells.
 - ⇒ Islet Cell Antibodies (ICA): found in up to 60 80% of patients with type 1 diabetes

Complications

- Microvascular complications include retinopathy, nephropathy, and neuropathy.
- Macrovascular complications include cerebrovascular, coronary artery, and peripheral vascular disease.

Diabetes mellitus: management of type 1

In newly diagnosed adults with type 1 diabetes, the first-line insulin regime should be a basal–bolus using twice-daily insulin detemir.

Diet

• Do not advise adults with type 1 diabetes to follow a low glycaemic index diet for blood glucose control.

Insulin

- Insulin injection regimen: offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice.
- For basal insulin:
 - ⇒ twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine is an alternative.
 - ⇒ once-daily ultra-long-acting insulin such as degludec, if there is a concern about nocturnal hypoglycaemia or for people who need help from a carer.
- For mealtime insulin: offer rapid-acting insulin <u>analogues</u> injected before meals, rather than rapid-acting soluble human or animal insulins.
- Insulin dose: normal insulin requirements are around 0.5–0.6 units/kg/day, split equally between background (basal) and mealtime (bolus) requirements
- Insulin dose adjustments
 - ⇒ During periods of illness: the TREND UK guidance advises that:
 - If blood glucose is less than 13 mmol/L and no ketones are present then insulin should be taken as normal.
 - If blood glucose is more than 13 mmol/L and ketones are present then
 insulin adjustment is needed. add 10% of the daily insulin dose as rapid
 acting insulin every four hours, and then four hourly glucose and ketone
 monitoring to guide ongoing dosage/management.
 - ⇒ **After alcohol or exercise** → reduce evening basal insulin by 25–50%.

Metformin

NICE recommend considering adding metformin if the BMI ≥ 25 kg/m²

Referral indication for islet or pancreas transplantation

- type 1 diabetes with recurrent severe hypoglycaemia that has not responded to other treatments
- type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy.

Monitoring

- Frequency of self-monitoring of blood glucose
 - ⇒ recommend testing at least 4 times a day, including before each meal and before bed.
 - ⇒ more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding.
 - □ during periods of illness, blood glucose and ketones should be checked at least every 4 hours.

Targets

Test	Targets
HbA1c	≤ 48 mmol/mol (6.5%)
fasting plasma glucose	5–7 mmol/litre on waking
	4–7 mmol/litre before meals
Post-prandial	5–9 mmol/litre (< 10)
during surgery or acute illness	5–8 mmol/litre
blood pressure	135/85 mmHg

Impaired fasting glucose and impaired glucose tolerance

- Impaired fasting glucose (IFG) is defined as fasting glucose ≥ 6.1 but < 7.0
 mmol/l
- Impaired glucose tolerance (IGT) is defined as fasting glucose < 7.0 mmol/l and OGTT 2-hour ≥ 7.8 mmol/l but < 11.1 mmol/l

Diabetes mellitus: Type 2 overview

Definition

 Type 2 diabetes mellitus is a progressive disorder defined by deficits in insulin secretion and increased insulin resistance

Epidemiology

- greater incidence among those of black and South Asian origin.
- Most are over 40yrs, but teenagers are now getting type 2 DM

Genetics

- Polygenic
- No HLA associations.
- Strong familial predisposition. Familial risks for developing diabetes
 - ⇔ Concordance between identical twins is higher in type 2 diabetes mellitus than type 1
 - \Rightarrow if one identical <u>twin</u> has type 2 diabetes, the risk in the unaffected twin \rightarrow 60 100 %.
 - ⇒ The incident diabetes risk in siblings and offspring of patients with type 2 diabetes is approximately 10%.

 \Rightarrow

Pathophysiology

- Peripheral insulin resistance
 - ⇒ Obesity→ ↓Adiponectin (secreted by adipocytes and involved in lipid catabolism) → insulin resistance (inversely correlated with the risk for diabetes).
 - ⇒ Central obesity → ↑free fatty acids → impaired insulin-dependent glucose uptake into hepatocytes, myocytes, and adipocytes
 - ⇒ ↑Plasminogen activator inhibitor 1 (↑in obesity & ↓ in weight loss → insulin resistance → type 2 diabetes mellitus.

- Beta cell dysfunction: accumulation of pro-amylin (islet amyloid polypeptide) in the pancreas → decreased endogenous insulin production
 - \Rightarrow Amyloid deposition $\rightarrow \downarrow$ islet cell number and function.
 - ⇒ The presence of <u>amyloid polypeptide on pancreatic histology</u> is highly suggestive of type 2 DM.
 - ⇒ Beta cell function is reduced by up to 70% at the point of type 2 diabetes diagnosis.
 - ⇒ The earliest manifestation of beta cell dysfunction occurs in the form of reduced and delayed postprandial early phase insulin secretion.
- Alpha cell dysfunction →↑ plasma glucagon
- **Secondary diabetes** (e.g. Haemochromatosis)

Risk factors

- Age, ethnicity and positive family history
- Conditions associated with insulin resistance: e.g., severe obesity, dyslipidemia
- Polycystic ovary syndrome
- Physical inactivity
- Hypertension
- History of gestational diabetes

Features

- The majority of patients are asymptomatic.
- Elderly patients may present in a hyperosmolar hyperglycemic state.
- Symptoms of hyperglycemia (Polyuria, Polydipsia Polyphagia)
- · Prone to recurrent infections
 - DM → Impaired neutrophil chemotaxis and phagocytosis → immunosuppression → recurrent infections
- 30% of patients presenting with acute coronary syndrome will have undiagnosed type 2 DM
- Increased concentrations of C peptide are a marker of increased colorectal cancer risk

Diagnosis: WHO criteria

- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL), or
- Plasma glucose ≥11.1 mmol/L (≥200 mg/dL) 2 hours after 75 g oral glucose, or
- Glycosylated haemoglobin (HbA1c) ≥48 mmol/mol (≥6.5%), or
- In a symptomatic patient, random plasma glucose of ≥11.1 mmol/L (≥200 mg/dL).
- Repeat confirmatory test is required in asymptomatic patients.

Diabetes diagnosis: fasting > 7.0, random > 11.1 - if asymptomatic need two readings

Beta cell mass

- Compared with subjects with normoglycaemia,
 - ⇒ beta cell mass is reduced by 50% in subjects with Impaired Fasting Glucose,
 - ⇒ by 70% in subjects with Type 2 diabetes, and
 - ⇒ over 90% in subjects with type 1 diabetes.

Diabetes UK suggests: 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes? →Small dense LDL molecules

Glycosylated haemoglobin (HbA1c)

Diabetes mellitus - HbA1c of 6.5% or greater is now diagnostic (WHO 2011)

Indications

- Diagnosis of diabetes mellitus and prediabetes state.
 - \Rightarrow Normal level \rightarrow < 42 mmol/mol (< 6%)
 - ⇒ An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes.
 - \Rightarrow Prediabetes \rightarrow 42 47 mmol/mol (6.0 6.4%)
 - **⇒** Diabetes mellitus → ≥ 6.5%
- Measure of long-term glycaemic control in diabetes mellitus.
 - ⇒ Reflects average blood glucose over the previous 2 3 months.

Follow up intervals

 NICE recommend 'HbA1c should be checked every 3-6 months until stable, then 6 monthly'.

Methods of reporting:

- Percentage vs mmol/mol
 - ⇒ A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

HBA1c (%)	IFCC-HbA1c (mmol/mol)
6	42
7	53
8	64
9	75

• Estimated average glucose

HBA1c (%)	Average plasma glucose (mmol/l)
5	5.5
6	7.5
7	9.5
8	11.5
9	13.5
10	15.5
11	17.5
12	19.5

Equations

- ⇒ New mmol/mol = [Old % 2.15] x 10.929
- ⇒ Old % = [New mmol/mol divided by 10.929] + 2.15
- ⇒ Average plasma glucose = (2 * HbA1c) 4.5

HbA1c targets

- For diabetic patient on lifestyle + metformin → 48 mmol/mol (6.5%)
- For diabetic patient on drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)
 → 53 mmol/mol (7.0%)

Unexpected or discordant HA1C values

- When there is a disparity between the A1C values and blood glucose values, we rely
 on the glucose values.
- Use frequent glucose monitoring . Fructosamine or glycated albumin may be useful alternatives.

The level of HbA1c therefore is dependent on:

- red blood cell lifespan
- · average blood glucose concentration

Falsely high A1C values

- · Low red cell turnover
 - ⇒ vitamin B12
 - ⇒ folate deficiency anemia.
- Splenectomy: spleen removes old RBCs. Not having a spleen increases RBC life span.

Falsely low A1C values

- · Rapid red cell turnover
 - Chronic hemolysis (eg, thalassemia, glucose-6-phosphate dehydrogenase deficiency);
 - ⇒ patients treated for iron, vitamin B12, or folate deficiency; and patients treated with erythropoietin.
- Blood transfusion (factitiously low A1C level)
- · Advanced chronic kidney disease, haemodialysis
- Alcohol consumption
- · Sudden weight loss

If A1C is higher than expected based on the mean glucose results

- Do fingerstick blood glucose levels between meals or short-term use of continuous glucose monitoring (CGM) to evaluate glucose patterns. One explanation is that the postprandial glucose is higher than pre-prandial test results that patients typically obtain.
- Exclude factors, which can falsely elevate the A1C (eq. low red cell turnover).

If the A1C is lower than expected based on the mean glucose results

- Do fingerstick blood glucose monitoring or CGM to detect nocturnal hypoglycemia, hypoglycemic unawareness, and/or frequent episodes of hypoglycemia. it is possible that blood glucose levels are low during times when testing is not being performed (such as undetected nocturnal hypoglycemia).
- Exclude factors, which can falsely decrease the A1C (eq, rapid red cell turnover).

Diabetes mellitus: management of type 2

Patient who is taking metformin for T2DM:

- if the HbA1c < 58 mmol/mol (7.5%): titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%).
- if the HbA1c rises to 58 mmol/mol (7.5%): add a second drug

General aim of management

 Reduce the incidence of macrovascular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

Risk factor modification

- Blood pressure
 - ⇒ target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
 - ⇒ ACE inhibitors are first-line
- Antiplatelets
 - ⇒ should not be offered unless a patient has existing cardiovascular disease
- Lipids
 - ⇒ only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin.
 - ⇒ The first-line statin of choice is atorvastatin 20mg on

HbA1c targets

- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on 'a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes'
- According to NICE guidelines, the HbA1c targets are now dependent on treatment:

· Lifestyle or single drug treatment

Management of T2DM	HbA1c target
Lifestyle alone or + metformin	48 mmol/mol (6.5%)
Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea)	53 mmol/mol (7.0%)

Be aware that there are other possible reasons for a low HbA1c level, for example, deteriorating renal function or sudden weight loss.

Self-monitoring of blood glucose

- Indications
 - ⇒ person is on insulin or oral medication that may increase their risk of hypoglycaemia while driving or operating machinery.
 - ⇒ evidence of hypoglycaemic episodes or to confirm suspected hypoglycaemia.
 - ⇒ pregnant, or planning to become pregnant.
 - ⇒ when starting treatment with oral or intravenous corticosteroids

Lifestyle modification

- Dietary advice
 - ⇒ Encourage high- fibre, low- glycaemic- index sources of carbohydrate, such as fruit, vegetables, wholegrains and pulses
 - ⇒ Include low- fat dairy products and oily fish
 - ⇒ Control the intake of foods containing saturated and trans fatty acids.
 - ⇒ limited substitution of sucrose- containing foods for other carbohydrate in the meal plan is allowable, but that they should take care to avoid excess energy intake.
 - ⇒ Discourage use of foods marketed specifically at people with diabetes
- Losing weight
 - ⇒ Initial target weight loss in an overweight person is 5-10%
- Physical activity

Drug treatment

- First line
 - offer standard release metformin
 - ⇒ titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%).
 - ⇒ If gastrointestinal side effects are not tolerated, then a trial of modified release metformin would be appropriate.
 - ⇒ If metformin is not tolerated at all then a dipeptidyl peptidase-4 inhibitor, sulfonylurea or pioglitazone would be indicated.
- Second line
 - ⇒ should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)
 - ⇒ there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) you now have a choice of 4 oral antidiabetic agents
 - ⇒ Second line for patient who tolerates metformin:
 - add one of the: Sulfonylurea, Gliptin, pioglitazone or SGLT-2 inhibitor (dual therapy)
 - If despite the dual therapy, the HbA1c remains above 58 mmol/mol (7.5%) or increased then triple therapy with one of the following combinations should be offered:
 - metformin + gliptin + sulfonylurea
 - metformin + pioglitazone + sulfonylurea
 - metformin + sulfonylurea + SGLT-2 inhibitor
 - metformin + pioglitazone + SGLT-2 inhibitor
 - OR insulin therapy should be considered
 - ⇒ Second line if metformin is not tolerated or contraindicated:
 - Consider one of the: Sulfonylurea, Gliptin or pioglitazone
 - if the HbA1c has risen to 58 mmol/mol (7.5%) then add one of the following (Dual therapy):
 - gliptin + pioglitazone
 - gliptin + sulfonylurea
 - pioglitazone + sulfonylurea
 - if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy
- Third line
 - ➡ If triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
 - BMI ≥ 35 kg/m² and specific psychological or other medical problems associated with obesity or

 BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities.

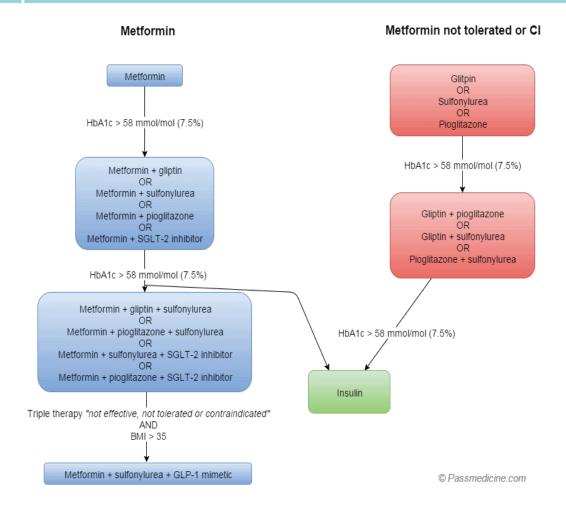
Starting insulin

- If HbA1c remains > 58 mmol/mol (DCCT = 7.5%) inspite of maximum tolerated oral therapy, then consider human insulin
- Metformin should be continued. In terms of other drugs NICE advice: 'Review the continued need for other blood glucose lowering therapies'
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need.
- Consider using insulin detemir or insulin glargine as an alternative to NPH insulin, if:
 - the person needs assistance to inject insulin, so as to reduce the frequency of injections from twice to once daily.
 - ⇒ recurrent symptomatic hypoglycaemic episodes
 - ⇒ the person need twice- daily NPH injections in combination with oral glucose- lowering drugs.
- Consider starting **both NPH and short- acting insulin** (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either: separately or as a pre-mixed (biphasic) human insulin preparation.
- Consider pre-mixed (biphasic) preparations that include short- acting insulin analogues, rather than pre- mixed (biphasic) preparations that include short- acting human insulin preparations, if:
 - ⇒ a person prefers injecting insulin immediately before a meal or
 - ⇒ hypoglycaemia is a problem or
 - ⇒ blood glucose levels rise markedly after meals.
- For patients who are on pre-mixed (biphasic) insulin and uncontrolled blood glucose, consider:
 - ⇒ further injection of short-acting insulin before meals **OR**
 - change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine.

Special considerations

- If the patient is at risk from hypoglycaemia (or the consequences of) then a DPP-4 inhibitor
 or thiazolidinedione should be considered rather than a sulfonylurea
- Meglitinides (insulin secretagogues) should be considered for patients with an erratic lifestyle
- You can consider using sitagliptin or a thiazolidinedione instead of insulin if there
 would be employment (eg: truck driver), social, recreational, or personal issues.
- In patients with diabetes starting thyroxine, doses of antidiabetic drugs including insulin
 may need to be increased.

<u>Diabetes associated with pancreatitis</u> is due to damage to the endocrine pancreas and associated lack of insulin. the patient's presentation: thin, with symptoms of insulinopaenia. As such, exogenous insulin replacement is the only appropriate intervention



Which laboratory test results would be most significantly associated with an increased incidence of cardiovascular disease in type 2 diabetics?

Raised proinsulin levels

January 2013 exam: A taxi driver with type 2 DM, on metformin and the dose was titrated up. His HbA1c one year ago was 75 mmol/mol (9%) and is now 69 mmol/mol (8.5%). His BMI 33 kg/m². What is the most appropriate next step in management?

Add sitagliptin (because DPP-4 inhibitors are weight neutral & no risk of hypoglycaemia)

September 2010 exam: H/O (T2DM) & bladder cancer on gliclazide and atorvastatin. A recent trial of metformin was unsuccessful due to gastrointestinal side-effects. He works as an accountant; is a non-smoker his BMI is 31 kg/m². HisHbA1c = 62 mmol/mol (7.8%) What is the most appropriate next step in management?

 Add sitagliptin (Pioglitazone is contraindicated in bladder cancer and may contribute to his obesity. he does not meet the NICE body mass index criteria of 35 kg/m².)

Biguanides (metformin)

Metformin should be titrated slowly, leave at least 1 week before increasing dose

Mechanism of action

- Inhibits mitochondrial glycerophosphate dehydrogenase (mGPD) → ↓ hepatic gluconeogenesis and intestinal glucose absorption
- Increases peripheral insulin sensitivity → ↑ peripheral glucose uptake and glycolysis

Indications

- type 2 diabetes mellitus
- polycystic ovarian syndrome
- · non-alcoholic fatty liver disease

Action of metformin in polycystic ovary syndrome:

Advantages

- Glycemic efficacy: lowers HbA1c by 1.2-2% over 3 months
- Weight loss
- · No risk of hypoglycemia
- · Beneficial effect on dyslipidemia
- Reduce macrovascular complications and death (superior to sulphonylureas and insulin in terms of macrovascular risk, e.g. myocardial infarction).

Adverse effects

- Gastrointestinal upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%
 - ⇒ commonly occur if not slowly titrated up.
 - ⇒ The BNF advises leaving at least 1 week before increasing the dose.
 - ⇒ modified release preparations reduce the risk further.
 - ⇒ High dose metformin interfere with the enterohepatic circulation of bile salts, leading to reduced reabsorption of bile salts from the ilieum → chronic diarrhoea.
- Vitamin B₁₂ deficiency
 - ⇒ Associated with long-term treatment with metformin
 - The possibility of metformin-associated B₁₂deficiency should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia.
- Lactic acidosis with severe liver disease or renal failure
 - ⇒ It is rare, although it remains important in the context of exams
 - ⇒ The patients usually have severe renal impairment.
 - ⇒ factors increases the risk of metformin lactic acidosis:
 - Tissue hypoxia, e.g. recent myocardial infarction, sepsis, acute kidney injury and severe dehydration.

- The (BNF) states that there should be a six week "cooling off" period post-MI before the commencement or recommencement of metformin.
- Contrast radiography. : metformin should be discontinued on the day of the procedure and for 48 hours thereafter
- Excess alcohol intake
- Drugs: Cyclosporin, aminoglycosides, cimetidine (Metformin is excreted by the renal tubules and this process can be inhibited by cimetidine, but not the other H2 receptor antagonists).
- ⇒ The mainstay of treatment is rehydration.
- ⇒ correction of acidosis with 8.4% sodium bicarbonate.
- ⇒ Patients with <u>resistant acidosis</u> should be considered for <u>haemodialysis</u>, <u>which</u> also clears <u>metformin</u>.
- Despite aggressive treatment, mortality still 50%.

High dose (> 2 gm daily) **interferes with enterohepatic circulation of the bile salts** (Bile salt malabsorption) → diarrhoea

Contraindications

- · Chronic kidney disease:
 - NICE recommend that the dose should be reviewed if the creatinine is > 130 mmol/l (or eGFR < 45 ml/min) (reduce the those and monitor renal function every three months) and stopped if the creatinine is > 150 mmol/l (or eGFR < 30 ml/min) (stage four chronic kidney disease (CKD 4)</p>
- Alcohol abuse is a relative contraindication → ↑risk of lactic acidosis
- Intravenous iodinated contrast medium
- Heart failure (NYHA III and IV), respiratory failure, shock, sepsis
- Alcoholism

<u>Sulphonylureas</u>

Mechanism of action

Block ATP-sensitive potassium channels (K_{ATP}) of the pancreatic β cells → depolarization of the cell membrane → calcium influx → insulin secretion

Side effects

- Life-threatening hypoglycemia; increased risk with the following :
 - ⇒ Age over 65 years
 - ⇒ Simultaneous intake of CYP2C9 inhibitors (e.g., amiodarone, trimethoprim, fluconazole)
 - ⇒ Patients with renal failure
 - ⇒ more common with long acting sulphonylureas such as chlorpropamide and glyburide (glibenclamide).
- Weight gain
- syndrome of inappropriate ADH secretion (SIADH)
- bone marrow suppression
- · liver damage (cholestatic)
- photosensitivity
- Hematological changes: granulocytopenia, hemolytic anemia

- Chlorpropamide & tolbutamide → disulfiram-like reaction following alcohol intake (alcohol intolerance).
 - ⇒ **alcohol intake** with Chlorpropamide & tolbutamide → inhibits aldehyde dehydrogenase (the enzyme responsible for the metabolism of acetaldehyde) → accumulation of toxic acetaldehyde → disulfiram-like effect (a drug used to treat alcoholism) → (**facial flushing**, erythema, paraesthesia of the extremities, nausea and vomiting, tachycardia, and hypotension).

Contraindications

- Pregnancy and breast feeding
- Severe cardiovascular comorbidity
- Severe liver and kidney failure
- Obesity
- Beta blockers (can mask hypoglycemic symptoms while lowering serum glucose levels)

The combination of beta-blockers and hypoglycemia should be avoided:

 Beta-blockers may mask the warning signs of hypoglycemia (e.g., tachycardia) and decrease serum glucose levels even further.

Agents

Glibenclamide

- ⇒ long-acting sulfonylurea
- ⇒ associated with a greater risk of hypoglycaemia, therefore, should be avoided in the elderly, and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead
- ⇒ Renally excreted: renal impairment →↑ risk of hypoglycaemia

Gliclazide

- ⇒ intermediate half-life of around 11 hours.
- ⇒ causes less hypoglycemia than other sulfonylureas.
- ⇒ extensively metabolised within the liver by CYP2C9. Renal clearance accounts for only 4% of total drug clearance. In CKD stage 1, 2, 3 (eGFR > 30 mL/min) gliclazide can be used safely, in patients with severe CKD → reduced dose can be used
- ⇒ gliclazide action can be potentiated predominantly by two mechanisms:
 - Displacement of the drug from plasma proteins to give freer (unbound) drug some agents such as aspirin can do this, and
 - Interference with the hepatic metabolism of the drug (e.g fluconazole)

Glipizide

- metabolized by the liver into inactive metabolites and therefore, renal insufficiency does not affect the drug's clearance.
- the best choice of sulfonylureas in a patient with renal impairment (no need for dose adjustment).

Chlorpropamide

- ⇒ has a higher side effect profile
- ⇒ may produce a syndrome of inappropriate anti-diuretic hormone (ADH) secretion.

Sulphonylurea provide microvascular benefits, but NO benefit was demonstrated for macrovascular outcomes (cardiovascular disease), in contrast to metformin.

Sulphonylurea overdoses:

In sulphonylurea overdoses, if the patient remains hypoglycaemic despite infusion of sufficient glucose, consider administration of octreotide (a somatostatin analogue which lowers insulin levels and thus raised blood glucose)

Meglitinides

Meglitinides - stimulate insulin release - good for erratic lifestyle

Meglitinides (nateglinide and repaglinide) \rightarrow increase postprandial insulin release specifically

Agents

- Repaglinide
- Nateglinide

Action \rightarrow closure of the β -cell K+-ATP channel.

- Short-acting insulin secretagogues
- Blockage of ATP-sensitive potassium (K_{ATP}) channels of the pancreatic beta cells → depolarization of the cell membrane → calcium influx → insulin secretion
- Act like sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site of the pancreatic channel.

Indications

 useful for post-prandial hyperglycaemia or an erratic eating schedule, as patients take them shortly before meals

Advantages

- The shorter action of duration result in less weight gain compared to sulphonylureas.
- Nateglinide is useful for shift workers and patients who tend to fast for a period of time because doses can be skipped when meals are missed. In these patient groups there may be a lower incidence of hyperglycaemia.
- Repaglinide can be used even in CKD stages 4 and 5 without dose reduction.

Adverse effects

weight gain and hypoglycaemia (less so than sulfonylureas)

Thiazolidinediones (glitazones, insulin sensitizers)

Mechanism of action: Peroxisome Proliferator Activated Receptor (PPAR) gamma agonists → increase peripheral insulin sensitivity

Glitazones are agonists of PPAR-gamma receptors, reducing peripheral insulin resistance

A major function of peroxisomes is beta-oxidation of fatty acids

(PPAR-γ) agonists increase the metabolism of free fatty acids

Agents

- Pioglitazone
- Rosiglitazone: was withdrawn in 2010 following concerns about cardiovascular side-effect profile.

Pioglitazone metabolism

mainly by CYP2C8 cytochrome P450 enzyme pathway

Mechanism of action

- Agonists to the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) receptor → ↑ transcription of genes involved in glucose and lipid metabolism → ↑ levels of adipokines such as adiponectin and insulin sensitivity → ↑ storage of fatty acids in adipocytes, ↓ products of lipid metabolism (e.g., free fatty acids) → ↓ free fatty acids in circulation → ↑ glucose utilization and ↓ hepatic glucose production.
 - ⇒ Metformin also boosts insulin sensitivity, but pioglitazone has more effect on peripheral insulin resistance.

PPAR-gamma receptor

- · an intracellular nuclear receptor.
- · Its natural ligands are free fatty acids
- it is thought to control adipocyte differentiation and function.
- activated by free fatty acids and thiazolinediones such as pioglitazone.

Indications

- may be considered as monotherapy in patients with severe renal failure and/or contraindications for insulin
- **NICE guidance advice that:** only continue **thiazolidinediones** if there is a reduction of > 0.5 percentage points in HbA1c in 6 months

Advantages

- Glycemic efficacy: lowers HbA1c by 1% in 3 months
- Favorable effect on lipid metabolism: ↓ triglyceride, ↓ LDL, ↑ HDL
- · No risk of hypoglycemia
- associated with the lowest rate of secondary beta-cell failure. Sulfonylureas are associated with the highest rate

Side effects

- ↑ Risk of heart failure
- ↑ Risk of bone fractures (osteoporosis). due to reduced osteoblast activity → reduced bone mineral density.
- · Fluid retention and edema
 - ⇒ the risk of fluid retention is increased if the patient also takes insulin , or other drugs that cause fluid retention (for example, NSAIDs, calcium antagonists)
- · Weight gain
- Rosiglitazone: ↑ risk of cardiovascular complications like cardiac infarction or death
- Bladder cancer
- liver impairment: monitor LFTs

Contraindications

- Congestive heart failure (NYHA III or IV)
- Liver failure
- Pioglitazone: history of bladder cancer or active bladder cancer; macrohematuria of unknown origin

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Thiazolidinediones are associated with an increased risk of bladder cancer

Pioglitazone may cause fluid retention

Insulin: Basics

Structure

 Insulin is a peptide hormone, composed of 51 amino acids. It is a dimer of an A-chain and a B-chain, which are linked together by disulfide bonds.

Production

• Insulin is produced in the pancreatic beta cell by proteolytic cleavage from pro-insulin resulting in **c-peptide** which is secreted together with **insulin in a 1:1 molar ratio**.

Secretion

- Insulin is stored in secretory granules
- Released by beta cells as a result of increased intracellular calcium.
- Released in pulses about every 9-13 minutes.
 - ➡ This pulsing release mechanism is important because it is thought that this keeps cells sensitive to insulin.
 - this is one of the first things that disappears when insulin sensitivity disappears.
- Secreted in response to hyperglycaemia

C-peptide

- a protein cleaved from proinsulin when it is activated.
- has a longer half-life than insulin, and thus is a useful measure of insulin secretion (it is more accurate than measuring insulin itself).
- The level of this can be measured in the urine.

Insulin and C peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

Functions

- Insulin binds to insulin receptors (a type of tyrosine kinase receptor) located in various
 tissues in the body → acts as an anabolic hormone in target tissues (e.g., liver, skeletal
 muscle, adipose tissue).
- Carbohydrate metabolism
 - ⇒ Stimulate Glycogenesis (glycogen synthesis from glucose by glycogen synthase, and glycogen branching enzyme. Triggered by high serum insulin concentrations.) in muscle and liver
 - ⇒ **Stimulate** Glycolysis (converts glucose to pyruvate and produces ATP and NADH as byproducts.) in adipose and muscle
 - ⇒ Inhibits Glycogenolysis (breakdown of glycogen by glycogen phosphorylase)
 - ⇒ Inhibits Gluconeogenesis (produces glucose from noncarbohydrate substances such as amino acids, triglycerides, and glycerol.) (Insulin inhibit pyruvate carboxylase which used in gluconeogenesis)
 - ⇒ Inhibits Production and release of glucagon
- Lipid metabolism
 - ⇒ **Stimulate** Lipid synthesis and triglyceride storage in adipose tissue
 - ⇒ Inhibits Lipolysis (breakdown of lipids)
 - ⇒ Inhibits Ketogenesis (production of ketone bodies by HMG-CoA synthase).

- · Protein metabolism
 - ⇒ **Stimulate** Protein synthesis in muscle tissue
 - ⇒ Stimulate Uptake of amino acids
 - ⇒ Inhibits Proteolysis
- Increases cellular uptake of potassium (via stimulation of Na+/K+ ATPase pump)

Insulin therapy

Insulin types

- Rapid-acting insulin analogues (Aspart, Lispro, Glulisine)
 - ⇒ Onset: 5 mins
 - ⇒ Peak: 1 hour
 - ⇒ Duration: 3-5 hours
 - ⇒ Reduces the chance of between-meal hypoglycaemia.
 - ⇒ Useful for reducing postprandial hypoglycaemia because their profile is more in keeping with physiological insulin release.
 - ⇒ If there is a pre-lunch hyperglycaemia, that means there is a significant post-breakfast peak in glucose levels. As such, the best management → breakfast time injection of rapid acting insulin.
- Short-acting insulins (Actrapid, Humulin S)
 - ⇒ Onset: 30 mins
 - ⇒ Peak: 3 hours
 - ⇒ Duration: 6-8 hours
 - ⇒ may be used as the bolus dose in 'basal-bolus' regimes
 - ⇒ "Standard insulin" for lowering blood glucose levels in an acute setting
 - ⇒ Intravenous therapy available
- Intermediate-acting insulins (Isophane [NPH])

 - ⇒ Peak: 5-8 hours
 - ⇒ Duration: 12-18 hours
 - ⇒ NICE guidelines advise that, in general, a humane isophane insulin is the firstline recommended insulin in type 2 diabetic.
- Long-acting insulins (Determir, Glargine)
 - ⇒ Onset: 1-2 hours
 - ⇒ Peak: Flat profile
 - ⇒ Duration: Up to 24 hours
 - ⇒ The main advantage → Reduced nocturnal hypoglycaemia
 - ⇒ might be useful in someone who struggles to inject a twice a day NPH insulin to reduce the frequency of injections to once a day (e.g. someone who requires assistance to inject from a career or district nurse).
 - ⇒ suitable for providing a basal level of insulin which attempts to mimic the normal physiological state.
 - In which situations does insulin glargine have the clearest advantage over isophane?
 - In patients with type-1 diabetes who have significant nocturnal hypoglycaemia on isophane
 - ⇒ NICE only recommends use of insulin glargine in patients who have significant hypoglycaemia on isophane insulin
 - ⇒ Detemir is the only long-acting insulin that is <u>soluble in the bottle as well as</u> under the skin, possibly allowing for more consistent absorption.

- Detemir can be administered with other forms of insulin, unlike insulin glargine, which cannot be mixed with other insulins or IV fluids due to its acid vehicle.
- ⇒ **Degludec** a long-acting insulin.
 - Onset: ~1 hour
 - Half-life elimination: ~25 hours (has the highest half-life)
 - Time to peak: 9 hours

Rapid-acting insulins are your favorite GAL (Glulisine, Aspart, Lispro).

Degludec

A patient with recurrent admissions for DKA secondary to missing doses can be started on degludec to reduce readmission rate.

Degludec has a much higher half-life than Detemir and therefore maintains a basal insulin level when the patient omits or forgets doses. This can prevent DKA.

Intravenous insulin is the optimal management of high blood sugar in acute myocardial infarction.

Insulin prescription

Starting dose

- ⇒ The guidelines recommend starting with either morning or evening long-acting insulin, or with **bedtime intermediate acting insulin**.
- 0.2 U/kg or a flat dose of 10 U is the recommended starting dose for intermediate acting insulin.

Targets

- \Rightarrow Fasting and pre-prandial glucose levels \rightarrow 4-7 mmol/L.
- ⇒ Post-prandial glucose levels : less than 10 mmol/L.
- ⇒ In hospitalised patients the Joint British Diabetes Societies for Inpatient care (JBDS) suggest a target blood glucose of 6-10mmol/L

Monitoring

- If patients are not using insulin, sulphonylureas or glinides (repaglinide or netaglinide), then the ADA/EASD consensus does not recommend selfmonitoring of blood glucose levels.
- ⇒ Once daily long-acting insulin taken at night is monitored using pre-breakfast fasting glucose measurements. If fasting levels are in range yet the HbA_{1c} is elevated, post-prandial monitoring is recommended.

Dose adjustment

- ⇒ Pre-prandial glucose: Mainly affected by the basal insulin dose
- ⇒ Postprandial glucose is mainly affected by meal intake and prandial insulin dose.
- At least three consecutive, self-monitored fasting glucose readings should be used to adjust doses (i.e. three days minimum between dose adjustments).
- ⇒ Up-titration
 - increase 2 U of insulin every three days until fasting glucose is in the target range of 3.9-7.2 mmol/L. If the fasting plasma glucose is >10 mmol/L, → uptitration schedule of 4 U every three days can be used.
- □ Down-titration
 - Reduce insulin dose in steps of 20% if hypoglycaemia occurs.

Insulin in renal failure

⇒ The dose of exogenous insulin is reduced 25% when eGFR is 10-50 mL/min and 50% when eGFR is < 10 mL/min

the most appropriate initial insulin regime for young patient after being diagnosed with new onset Type1 DM \rightarrow Meal time Actrapid and insulatard at night.

Insulin side-effects

- Hypoglycaemia
- · Weight gain
- Hypokalemia
- · Lipodystrophy at the injection site
 - ⇒ typically presents as atrophy of the subcutaneous fat
 - ⇒ can be prevented by rotating the injection site

Mixtard- associated nocturnal hypoglycemia

- This is because the insulatard component of the Mixtard peaks about 6 h after it has been given. This, along with some residual actrapid activity, gives an excess of insulin in the middle of the night, leading hypoglycaemia.
- Split evening insulin so take actrapid before evening meal and insulatard before bedtime

Hypoglycaemic episodes which occur during the day in a patient takes a basal bolus insulin regime of long-acting insulin (Insulatard®) and short-acting insulin (Actrapid®) with each meal:

- the most appropriate next step → Refer for Dose Adjustment For Normal Eating education (DAFNE)
- the next step after DAFNE, should hypos persist, would be continuous glucose
 monitoring, to learn more about fluctuations in serum blood glucose over the course of the
 day.
- those patients who have problems with nocturnal hypoglycaemia → changing insulatard to insulin glargine

What is the most appropriate initial advice with respect to adjusting prandial insulin dose?

• 1 unit of insulin per 10 grams of dietary carbohydrate

Glucagon-like peptide-1 (GLP-1)

Incretins increase insulin release and decrease glucagon secretion from the pancreas. DPP-IV metabolizes GLP. Inhibiting DPP-IV maintains high levels of GLP.

GLP-1 : Site of synthesis → Small intestinal L cells

Incretin effect

- Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), produced by the L-cells of the ileum →↑ insulin release (more than if the same load is given intravenously), ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight) this known as the incretin effect.
- This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Glucagon-like peptide-1 (GLP-1)

- Production
 - ⇒ glucagon-like peptide-1 (GLP-1), a hormone produced by the L-cells of the <u>ileum</u> in response to an oral glucose load
- Effects in glucose homeostasis
 - ⇒ Glucose-dependent stimulation of insulin secretion
 - ⇒ Reduction of gastric emptying
 - ⇒ Reduction of inappropriate glucagon secretion
 - ⇒ Weight loss
- Regulation of GLP-1
 - ⇒ Increasing GLP-1 levels, either by:
 - administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) OR
 - inhibiting its breakdown (dipeptidyl peptidase-4, DPP-4 inhibitors the gliptins), is therefore the target of two recent classes of drug.

GLP is a confusing misnomer: Glucagon raises glucose and FFA levels. GLP decreases glucagon.

Glucagon-like peptide-1 (GLP-1) analogs

Exenatide = Glucagon-like peptide-1 (GLP-1) mimetic

Exenatide causes vomiting

Agents: Exenatide, Liraglutide

- Liraglutide VS Exenatide
 - ⇒ Liraglutide is given once a day (long-acting) whereas Exenatide is given twice daily (has a half-life of around 2.5 hours)
 - ⇒ Liraglutide <u>can be used in renal impairment</u> with an estimated glomerular filtration rate [eGFR] as low as 30 mL/min/1.73 m2. Exenatide are cleared via renal excretion and is therefore not recommended in patients with an eGFR < 30.</p>

Mechanism of action

Incretin effect: Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), produced by the
L-cells of the <u>ileum</u> →↑ insulin release (more than if the same load is given
intravenously), ↓ glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓
weight).

- GLP-1 agonists (Incretin mimetic drugs) →↑GLP-1 levels → ↑ insulin secretion, ↓
 glucagon secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight)
- Metabolic effects
 - ⇒ increase insulin secretion
 - ⇒ inhibit glucagon secretion.
 - ⇒ inhibits glucose production in the liver
 - ⇒ slows gastric emptying →Suppresses appetite

Indications

- NICE state that: Consider adding exenatide to metformin and a sulfonylurea if:
 - ⇒ BMI ≥ 35 kg/m in people of European descent and there are problems associated with high weight, or
 - ⇒ BMI < 35 kg/m and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.

Advantages

- Improve glycaemic control: lowers HbA1c by 0.5–1.5% over 3 months
- No risk of hypoglycemia
- **Promote weight loss** (≈ 6% weight loss over a 6 month period).

Administration

NICE like patients to have achieved a 1% reduction in HbA1c (11 mmol/mol) and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

Adverse effects

- nausea and vomiting (the major adverse effect).
- Acute pancreatitis in some patients.

The preferred pathway for glucose management according to the NICE guidelines is to add insulin to the combination of metformin and a sulphonylurea. However, where weight is of particular concern (BMI >35), exenatide may be considered as an alternative. It can also be used where insulin would interfere with a patient's occupation.

When to choose exenatide as an alternative to insulin or sulphonylurea as first choice add-in options to metformin?

- morbid obesity
- or risk of hypoglycaemia, (eg : HGV drivers)

Current NICE guidance suggests the use of GLP-1 mimetics only if BMI is above 35 and there are specific medical or psychological problems associated with high body weight.

Sign guidelines 2017: For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)

Gliptins = Dipeptidyl peptidase-4 (DPP-4) inhibitors

Agents

Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin and Alogliptin

Action

- Incretin effect: Oral glucose load → ↑ glucagon-like peptide-1 (GLP-1), produced by the
 L-cells of the <u>ileum</u> → GLP-1 degradation via the enzyme DPP-4 → end of the GLP-1
 effect.
- DPP-4 inhibitors (Incretin mimetic drugs) bind to the GLP-1 receptors inhibiting the
 DPP-4 that breaks down GLP-1 →↑GLP-1 levels → ↑ insulin secretion, ↓ glucagon
 secretion, slow gastric emptying (↑ feeling of satiety, ↓ weight)

Indications

- Can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, or other glucose-lowering agents.
 - e.g linagliptin might be a good choice as initial therapy in a patient with chronic kidney disease or who is at particularly high risk for hypoglycemia.
- Only recommended as second-line therapy with metformin if patients are at significant risk of hypoglycaemia or its consequences (e.g. older patients, those working at heights or heavy machinery, isolated patients) or if a sulphonylurea is not tolerated or contraindicated.
- can be considered as add-on drug therapy for patients who are inadequately controlled on metformin, a thiazolidinedione, sodium-glucose co-transporter-2 (SGLT2) inhibitor, or a sulfonylurea.
- NICE guidelines suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione
- **NICE guidelines recommend:** continue DPP-4 inhibitor only if there is a reduction of > 0.5 percentage points in HBA1c in 6 months.

Advantages

- Oral preparation
- · Well tolerated with no increased incidence of hypoglycaemia
- · Do not cause weight gain
- We can use them all in CKD but with dose adjustment (Only <u>linagliptin</u> does not need dose adjustment in any stage of CKD)
- Linagliptin is preferred in patients with chronic kidney disease [eGFR] <30 mL/min/1.73 m²)

Side effects

- Gl disturbance (nausea, flatulence, diarrhoea and constipation) (because DPP-4 inhibitor delays gastric emptying).
- Acute pancreatitis (insufficient data) still under investigation but is to be discontinued in the event of pancreatitis.
- Saxagliptin associated with increased incidence of heart failure.
- · Increased risk of upper respiratory tract infections.

Sodium-glucose cotransporter 2 inhibitors (gliflozins)

Empagliflozin has been shown to reduce cardiovascular mortality

Examples

• Include canagliflozin, dapagliflozin and empagliflozin

Mechanism of action

reversible inhibition of SGLT-2 in the proximal convoluted tubule of the kidney → ↓ glucose reabsorption → glycosuria and polyuria.

Indications

- Empagliflozin or canagliflozin may play a role in patients with overt cardiovascular diseases (CVD) or heart failure not reaching glycemic goals with metformin and lifestyle modifications
- may have a role <u>as a third agent in those who cannot or will not take insulin</u>, when full
 doses of metformin and a sulfonylurea have not produced satisfactory metabolic control, or
 <u>in patients in whom risk of hypoglycemia is high</u> (frail, older adults) or <u>in whom avoidance of</u>
 weight gain is a priority.

Advantages

- Glycemic efficacy: lowers HbA1c by 0.6% over 3 months
- Promotes weight loss (modest calorie spillage into the urine)
 - there for it is better than gliptins in obese patient who does not achieve control by metformin
- ↓ Blood pressure (Sodium loss → fall in BP)
- J Risk of cardiovascular mortality in patients with type 2 DM and cardiovascular disease
- Reduce uric acid, which may over the longer term reduce nephropathy progression
- Do not usually cause hypoglycemia

Adverse effects

- Recurrent infections due to glucosuria
 - ⇒ Recurrent urinary infections (↑ glucose in the urine (Glycosuria) → predispose to bacterial growth)
 - ⇒ Genital infection (Vulvovaginal candidiasis): contra-indicated in patients with recurrent thrush.
 - ⇒ Necrotizing fasciitis of the perineum
- Diabetic ketoacidosis (patients may present with euglycaemic ketoacidosis)
 - \Rightarrow SGLT-2 inhibitors $\rightarrow \uparrow$ glucagon, $\rightarrow \uparrow$ lipid oxidation $\rightarrow \uparrow$ risk of ketoacidosis.
- Increased risk of bone fracture
 - \Rightarrow SGLT-2 inhibitors $\Rightarrow \uparrow PTH \rightarrow \uparrow \uparrow$ bone turnover $\rightarrow \uparrow$ risk of bone fracture.
 - \Rightarrow SGLT-2 inhibitors \Rightarrow \uparrow fibroblast growth factor (FGF-23) \rightarrow \downarrow vitamin D \rightarrow \uparrow \downarrow bone mineralisation.
- Acute kidney injury
- Dehydration → weight loss, orthostatic hypotension
- Increased total cholesterol, (both HDL and LDL)
- ↑ Risk of lower limb amputation: Empagliflozin is preferred rather than canagliflozin.
 Canagliflozin found to be associated with increased risk of lower limb amputation and fractures.

Sign guidelines (November 2017): In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit (currently empagliflozin and canagliflozin) should be considered.

Contraindications

- Renal Impairment: eGFR <30 mL/minute/1.73 m2: Use is contraindicated.
- Recurrent urinary tract infections (e.g., in patients with anatomical or functional anomalies
 of the urinary tract)

Alpha-glucosidase inhibitors

Overview

- These are acarbose, miglitol and voglibose.
- Not usually used as first-line therapy, because of modest efficacy and poor tolerance.

Mechanism of action

 inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides and thereby slow absorption of glucose and reduce postprandial blood glucose concentration.

Advantages

- They may be used as part of a combination regimen in people who consume highcarbohydrate diets and have high postprandial glucose levels.
- reduction in risk of new onset type 2 diabetes and cardiovascular events.

Side effects

- Abdominal pain, flatulence and diarrhea (Using glucosidase inhibitors is like making a person lactose intolerant).
 - ⇒ Mechanism of diarrhoea: Alpha-glucosidase inhibitors → block glucose absorption → the sugar remains in the bowel → bacteria eat the glucose, and cast off gas and acid.

Diabetic ketoacidosis (DKA): Overview

Epidemiology

 Approximately 25% of patients with type 1 diabetes will first present in diabetic ketoacidosis

Pathophysiology

- Osmotic diuresis and hypovolemia
 - \Rightarrow Insulin deficiency \rightarrow hyperglycemia \rightarrow hyperosmolality \rightarrow osmotic diuresis and loss of electrolytes \rightarrow hypovolemia
- · Metabolic acidosis with increased anion gap
 - ⇒ Insulin deficiency → ↑ lipolysis → ↑ free fatty acids → hepatic ketone production (ketogenesis) → ketosis → bicarbonate consumption (as a buffer) → high anion gap metabolic acidosis

- ⇒ Lack of insulin → ↑cortisol, catecholamines and glucagon → ↑ fatty acid metabolism → ↑ beta-hydroxybutyrate → acetoacetate → urine ketone
- ⇒ Insulin withdrawal → initial acute rise in glucagon concentrations → Hepatic glucose production rises rapidly over the first 2 4 hours reaching a plateau after around 4 hours

Intracellular potassium deficit

⇒ Insulin deficiency → hyperosmolality → K+ shift out of cells + lack of insulin to promote K+ uptake → intracellular K+ depleted → total body K+ deficit despite normal or even elevated serum K+ (Total body potassium is reduced by up to 500 mmol)

What is the primary cause of ketoacidosis in type 1 diabetes?

Lipolysis

Causes

- Precipitating factors leading to diabetic ketoacidosis (DKA) are:
 - ⇒ Infection (30-40%) The most common precipitating factor
 - ⇒ Non-compliance with treatment (25%)
 - ⇒ Newly diagnosed diabetes (10-20%)
 - ⇒ Alterations to insulin dose (13%)
 - ⇒ Myocardial infarction (< 1%)
- The drugs implicated in precipitating diabetes as well as diabetic ketoacidosis.
 - ⇒ atypical antipsychotics such as olanzapine
 - ⇒ thiazide diuretics
 - ⇒ beta sympathomimetics, and
 - ⇒ steroids.

Features

- abdominal pain
- · polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell) (Fruity odor)
- serum sodium is falsely low due to the osmotic load of glucose.
- Blood count:
 - ⇒ Platelet secretory activity is often increased in DKA, but aggregation decreased.
 - ⇒ Neutrophil count is also commonly raised and correlates with ketone body levels, so does not necessarily imply underlying infection.

Diagnostic criteria: All of these must be present to make the diagnosis:

- The 'D' a blood glucose of >11.0 mmol/L or known to have diabetes mellitus
- The 'K' a capillary or blood ketone of >3.0 mmol/L or significant ketonuria (2+ or more)
- The 'A' a bicarbonate of <15.0 mmol/L and/or venous pH <7.3

Association

A raised amylase in the absence of frank pancreatitis is common in patients with diabetic ketoacidosis (DKA), No specific management is required, and amylase falls with rehydration and control of blood glucose.

Very high glucose artificially drops sodium level → Pseudohyponatremia

Cause of hyperkalemia → transcellular shift of potassium out of the cell in exchange for hydrogen.

Cause of \downarrow total body K stores \rightarrow excess loss of solutes with water in the urine. Cause of hypokalemia during DKA treatment \rightarrow insulin drives potassium into cells with glucose.

Assessment of severity: presence of one or more of the following may indicate **severe DKA** (suggest intensive care admission):

- GCS < 12
- Oxygen saturation <92% on air
- Systolic blood pressure <90 mmHg
- Tachycardia (>100) or bradycardia (< 60 bpm)
- pH < 7
- Blood ketone > 6 mmol/L
- Bicarbonate < 5 mmol/L
- Anion gap >16 mmol/l. [Anion Gap = (Na+ + K+) (Cl- + HCO3-)]. Normal values are 8-12 mEq/L.
- Potassium < 3.5 mmol/L on admission

Differential diagnosis

- · Alcoholic ketoacidosis
 - Ketoacidosis without a raised glucose in a person with alcoholism is virtually diagnostic of alcoholic ketoacidosis.
 - ⇒ a careful history needs to be taken to differentiate it from euglycaemic DKA.
 - ⇒ If alcoholic ketoacidosis is suspected, then ß-hydroxybutyrate should be measured and not urine ketones, because acetoacetate production can be suppressed in alcoholic ketoacidosis.
- Starvation ketosis
 - ⇒ ↓carbohydrate intake →↓insulin secretion, → lipolysis and ketosis.
 - ⇒ because it is arises over a prolonged period,→ renal compensation → acid base and electrolyte disturbances are often minimal

Diabetic ketoacidosis (DKA): Management

Fluid replacement

- · Calculate fluid deficit
 - \Rightarrow mild to moderate DKA (indicated by a blood pH of 7.1 or above) \rightarrow 5% fluid deficit.
 - ⇒ severe DKA (indicated by a blood pH below 7.1) → 10% fluid deficit.
 - ⇒ Most patients with DKA are deplete around 5-8 litres.
- Calculate maintenance fluid requirement
 - ⇒ if they weigh less than 10 kg, give 2 ml/kg/hour
 - ⇒ if they weigh between 10 and 40 kg, give 1 ml/kg/hour
 - ⇒ if they weigh more than 40 kg, give a fixed volume of 40 ml/hour.
- Choose appropriate fluids
 - ⇒ Use 0.9% sodium chloride until the plasma glucose is below 14 mmol/litre. If the glucose falls below 14.0 mmol/L:
 - commence 10% glucose given at 125 ml/ hour alongside the 0.9% sodium chloride solution, so that the insulin infusion can be continued at a sufficient rate to clear ketones (for example, 6 units/hour, monitored for effect).

- In addition consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr.
- All fluids (except any initial bolus) administered with 40 mmol/litre potassium chloride unless they have renal failure.

Rate of fluid replacement

⇒ JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over:

Fluid	Volume
0.9% sodium chloride 1L	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours

⇒ Slower infusion may be indicated in young adults (aged 18-25 years →↑risk of cerebral oedema), elderly, heart or kidney failure.

Fluid deficit in DKA

- Assume a 5% fluid deficit in children and young people in mild or moderate DKA (indicated by a blood pH of 7.1 or above)
- Assume a 10% fluid deficit in children and young people in severe DKA (indicated by a blood pH below 7.1)

Insulin

- Insulin type
 - ⇒ Soluble infusion → intravenous infusion at **0.1 unit/kg/hour**.
 - ⇒ If patient normally takes **long acting insulin analogue (Lantus, Levemir) continue at usual dose and time.** In those newly diagnosed, then a long acting basal insulin should be commenced, at a dose of 0.25 units/Kg subcutaneously once daily.
- Best time for starting → NICE recommend to start insulin infusion 1–2 hours after beginning intravenous fluid therapy
- Rate of infusion (fixed rate insulin regime, not a sliding scale).
 - ⇒ 0.1 unit/kg/hr based on estimate of weight
 - ⇒ 50 units human soluble insulin (Actrapid or Humulin S) made up to 50 ml with 49.5 ml 0.9% sodium chloride solution (i.e. 1 unit /ml).
 - Once the glucose drops to <14 mmol/L then in addition to adding a 10% dextrose infusion consider reducing the rate of intravenous insulin infusion to 0.05 units/kg/hr to avoid the risk of developing hypoglycaemia and hypokalaemia</p>
 - ⇒ Insulin infusion rate should only be increased if blood ketones are not falling at >0.5 mmol/h, venous bicarbonate not increased by 3.0mmol/L/hour or capillary blood glucose not reduced by 3.0mmol/L/hour.

Correction of hypokalaemia

- As a result of both acidosis and insulin deficiency there is a total body potassium deficit
 of up to 1000 mmol.
- rehydration, insulin replacement and correction of acidosis resulting in further potassium loss with restoration of urine flow
- hypokalemia is a major cause of death in ketoacidosis.

· JBDS potassium quidelines

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
Over 5.5	Nil
3.5-5.5	40
Below 3.5	Senior review as additional potassium needs to be given

Other treatment

Bicarbonate

- ⇒ The role of bicarbonate in DKA is controversial. Generally not recommended.
- ⇒ The acidosis usually corrects itself once the fluid and electrolyte balance is restored.
- ⇒ There is no evidence to support bicarbonate use in a patient with a pH greater than 7.0
- ⇒ Intravenous bicarbonate should be given if the blood pH is lower than 6.9.
- ⇒ In practice for DKA, sodium bicarbonate is only really considered in the peri-arrest situation.

• Low-molecular weight heparin

DKA increased risk of venous thromboembolism because of volume depletion, hyperglycaemia and their decreased conscious level.

Monitoring

 Blood glucose should be assessed every hour but testing for urine ketones can be performed every 4 hours.

Assessment of treatment

- Targets
 - ⇒ Reduction of the blood ketone concentration by **0.5mmol/L/hour**
 - ⇒ Increase the venous bicarbonate by **3.0mmol/L/hour**
 - ⇒ Reduce capillary blood glucose by 3.0mmol/L/hour
- · If these targets rates are not achieved:
 - always check the insulin infusion pump malfunction (the correct insulin residual volume is present)
 - ⇒ then the FRIII rate should be increased by 1 unit/hr increments hourly until the targets are achieved.
- Expected time of DKA resolution
 - ⇒ It is unusual for DKA not to have resolved **by 24 hours** with appropriate treatment
- Indicators of DKA resolution: Resolution of DKA is defined as:
 - \Rightarrow pH > 7.3 units.
 - ⇒ bicarbonate > 15.0mmol/L; and
 - ⇒ blood ketone level < 0.6mmol/L (rather than < 0.3mmol/L), in order to avoid restarting the FRIII if the ketone level rebounds upon discontinuation of the FRIII</p>
- Unreliable indicators of acidosis resolution
 - Glucose level is not an accurate indicator of resolution of acidosis in ketoacidosis, so the acidosis resolution should be verified by venous gas analysis.
 - ⇒ <u>Do not rely on bicarbonate alone to assess the resolution of DKA</u> due to the possible hyperchloraemia secondary to large volumes of 0.9% sodium chloride infusion.
 - ↑↑ 0.9% sodium chloride infusion →↓HCO3 →hyperchloremic metabolic acidosis → difficulty is assessing whether the ketosis has resolved.

- hyperchloraemic acidosis may cause renal vasoconstriction → oliguria.
- ⇒ Do not rely on urinary ketone clearance to indicate resolution of DKA, because these will still be present when the DKA has resolved.

Euglycaemic DKA

- Definition: DKA in people known to have diabetes but where the glucose is normal, or not particularly raised.
- Causes
 - ⇒ partial treatment of DKA prior to admission
 - ⇒ use of the sodium-glucose cotransporter (SGLT) inhibitor drugs (e.g. dapagliflozin, canagliflozin, empagliflozin)
- **Treatment:** treated in exactly the same way as hyperglycaemic DKA.
 - 1) Initiate glucose 10% straight away at 125 ml/hr because the glucose is < 14 mmol/L</p>
 - ⇒ 2) Begin with 0.1units/kg/hr insulin rate
 - ⇒ 3) If glucose falling despite 10% glucose reduce to 0.5 units/kg/hr to avoid hypoglycaemia

SCE-question sample-mrcpuk.org:

The **non-improvement of the patient's clinical status** and biochemical findings suggest that the **metabolic acidosis is due to another reason** such as **sepsis**. The finding of a **raised lactate concentration** will provide further insights.

Typical deficits in DKA in adults:

- Water 100ml/kg
- Sodium 7-10mmol/kg
- Chloride 3-5mmol/kg
- Potassium 3-5mmol/kg

Resolution of DKA is defined as:

- pH > 7.3 units.
- bicarbonate > 15.0mmol/L; and
- blood ketone level < 0.6mmol/L (rather than < 0.3mmol/L), in order to avoid re-starting the FRIII if the ketone level rebounds upon discontinuation of the FRIII

At which time, a patient can be converted back to subcutaneous insulin?

After Resolution of DKA

Metabolic treatment targets

- Reduction of the blood ketone concentration by 0.5 mmol/L/hour
- Increase the venous bicarbonate by 3.0 mmol/L/hour
- Reduce capillary blood glucose by 3.0 mmol/L/hour
- Maintain potassium between 4.0 and 5.5 mmol/L

If these targets are not achieved, then the fixed rate intravenous insulin infusion (FRIII) rate should be increased by 1 unit/hr increments hourly until the targets are achieved.

Complications of DKA and its treatment

- Cerebral oedema
 - ⇒ The risk is highest in paediatric (1%) and adolescent patients and is rarer in adults.
 - - Exact pathogenic mechanism remains unknown multifactorial
 - †glucose → †osmolar gradient results in water shift from the intracellular fluid (ICF) to the extracellular fluid (ECF) space and contraction of cell volume.
 Correction with insulin and I.V fluids → rapid reduction in osmolarity → reversal of the fluid shift → cerebral edema.
 - ⇒ Features
 - headache
 - agitation or irritability
 - unexpected fall in heart rate
 - increased blood pressure.
 - deterioration in level of consciousness
 - abnormalities of breathing pattern, for example respiratory pauses
 - oculomotor palsies
 - pupillary inequality or dilatation.
 - ⇒ Treatment
 - mannitol (20%, 0.5–1 g/kg over 10–15 minutes) or hypertonic sodium chloride (3% over 10–15 minutes) to induce osmotic fluid shifts.
 - urgent treatment should be started when cerebral oedema is suspected and not be delayed whilst awaiting imaging.
- Thromboembolism
- Acute respiratory distress syndrome
- · Arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- Acute kidney injury (AKI): Transient AKI may occur in up to 50% of adults.
- Recovering DKA are at risk of hypophosphataemia
 - ⇒ weakness following treatment for DKA.
 - often arises as a side effect of insulin with cells forming ATP and taking up free phosphate to achieve this.

Prognosis

- The mortality rate associated with the modern management of DKA → 1-2%
- Specifically, mortality relates to cerebral oedema.

(SCE- question samples.mrcpuk.org)

A 26-year-old woman with **DKA**. After 24 hours of treatment with intravenous fluids, potassium and insulin, her normal subcutaneous insulin regimen was resumed. However, she felt nauseated and there was a concomitant increase in **blood ketones to 3.5 mmol/L** (<0.3). random plasma **glucose: 7.3 mmol/L**. **What is the most appropriate next step in management?**

- start glucose 10% with fixed-rate intravenous insulin
 - ⇒ A fixed-rate insulin infusion is recommended for faster resolution of DKA.
 - ⇒ If the blood glucose is below 14 mmol/L, it is necessary to administer intravenous infusion of 10% glucose in order to avoid hypoglycaemia and permit the continuation of fixed-rate intravenous insulin.

Hypoglycaemia

Definition

- In patients with diabetes: generally described as ≤ 3.9 mmol/L (≤ 70 mg/dL).
- It can be defined as "mild" if the episode is self-treated and "severe" if assistance by a third
 party is required.

Counter-regulatory responses in patients with hypoglycaemia and threshold for symptoms

- There is considerable variability in the serum glucose level at which a person will
 experience symptoms of hypoglycemia. Usually occurred by the time serum glucose
 concentration is < 2.8 mmol/L (50 mg/dL).
- Response mechanisms against hypoglycaemia in healthy patients:
 - ⇒ The first response is → insulin release inhibition. This occurs when plasma glucose reaches approximately 4 mmol/L.
 - ⇒ The second response is → counterregulatory hormone release (glucagon, adrenaline, noradrenaline, cortisol, and growth hormone). Occurs when glucose drops to 3.6-3.9 mmol/L.
- Recurrent hypoglycemia in diabetic patients → hypoglycemia-associated autonomic failure (HAAF) → changes in the counterregulatory response (e.g., decreased epinephrine release) → lower glucose threshold needed to trigger symptoms → asymptomatic hypoglycemia (for this reason, the initial symptom of hypoglycemia in patients with HAAF is often confusion.)

Epidemiology

- between 30 to 40 % of patients with type 2 diabetes experience symptomatic hypoglycaemia.
- The prevalence of severe hypoglycaemia is similar in patients with type 2 diabetes receiving insulin for more than 5 years to that in patients with type 1 diabetes

Causes

Diabetic patients: relative overdose of insulin or a noninsulin drug is the most common cause.

- Insulin-related
 - ⇒ Insulin excess or noninsulin drugs (e.g., sulfonylureas, meglitinides)
 - ⇒ Increased sensitivity to insulin (weight loss, ↑ activity/exercise)
 - ⇒ Decreased insulin clearance (renal failure)
- **Glucose-related** (missed meals, Exercise)
- Acute illness (sepsis, organ failure)

Nondiabetic patients

- Endogenous hyperinsulinism or IGF (insulinoma, Gastric bypass surgery (late dumping syndrome)
- Exogenous hyperinsulinism (self-administration of insulin/sulphonylureas)
- Critical illness (sepsis, organ failure)
- Liver failure
- Hormone deficiencies (hypopituitarism, adrenal insufficiency)
- Alcohol
- Autoimmune causes
 - ⇒ Insulin autoimmune syndrome (IAS)
 - ⇒ Anti-insulin receptor autoantibodies: Usually associated with autoimmune diseases like Sjögren syndrome and SLE.
- Drugs that cause hypoglycemia
 - ⇒ Nonselective beta blockers

- ⇒ Antimalarial drugs: quinine, chloroquine
- Antibiotics: sulfonamides, trimethoprim-sulfamethoxazole, fluoroquinolones
- ⇒ Antifungal drugs: pentamidine, oxaline
- ⇒ Analgesics: indomethacin, propoxyphene/dextropropoxyphene
- ⇒ Antihypertensive drugs: **ACE-inhibitors** → improve insulin sensitivity.
- ⇒ Antiarrhythmics: cibenzoline, disopyramide
- ⇒ **Low dose aspirin** → ↓prostaglandin synthesis → stimulate beta cell
- ⇒ Others: IGF-1, lithium, mifepristone, heparin, 6-mercaptopurine

Consider factitious disorder in patients with access to insulin and other diabetes medications (e.g., healthcare professionals), for whom there is no other obvious explanation for hypoglycemia.

Beta blockers can mask signs of hypoglycaemia.

Features

- · Neurogenic/autonomic
 - ⇒ Increased sympathetic activity: tremor, pallor, anxiety, tachycardia, sweating, and palpitations
 - □ Increased parasympathetic activity: hunger, paresthesias, nausea, and vomiting
- Neuroglycopenic
 - ⇒ Agitation, confusion, behavioral changes
 - ⇒ Fatigue
 - ⇒ Seizure, focal neurological signs
 - Nocturnal hypoglycaemia →vivid dreams →REM sleep disruption → daytime weakness and somnolence.
 - \Rightarrow Somnolence \rightarrow obtundation \rightarrow stupor \rightarrow coma \rightarrow death

Diagnosis → Whipple triad:

- ⇒ Low plasma glucose concentration
- ⇒ Signs or symptoms consistent with hypoglycemia
- ⇒ Relief of symptoms when plasma glucose increases after treatment

Standard work-up for hypoglycaemia:

- Laboratory (not test-strip) blood glucose measurement
- Insulin and C-peptide levels taken during the hypoglycaemic attack
 - ⇒ Hypoglycaemia + hyperinsulinaemia → insulin is the cause of hypoglycaemia.
 - ⇒ External insulin does not contain C-peptide, which is released from pancreatic islet with endogenous insulin.
 - \Rightarrow \uparrow Insulin + \downarrow C-Peptide \rightarrow insulin abuse
 - \Rightarrow ↑ Insulin + ↑ C-Peptide \rightarrow endogenous hyperinsulinism (e.g insulinoma, sulphonylurea)
- Sulphonylurea level (serum or urine)
- Liver function tests to rule out significant liver dysfunction
- Blood alcohol and alcohol history
- · Cortisol levels, with or without Synacthen testing
- Chest X-ray to exclude occult malignancy

Work-up for hypoglycaemia is not indicated in two occasions

- If the Whipple triad is not confirmed, no further workup is indicated.
- Hypoglycemia in diabetic patients is almost always due to acute illness and/or medications (e.g., insulin) and further workup is generally not indicated.

If both C-peptide and insulin are raised → Suggests endogenous insulin secretion.

 Request a plasma sulfonylurea screen is the most appropriate next step, and depending on the result of this, further investigation may be required.

↑ Insulin with ↓ C-Peptide level points to a diagnosis of insulin abuse → Exogenous insulin administration (as the C peptide is released with endogenous insulin). C-Peptide level ↑ with Sulfonylurea abuse

Management

- For patient who are able to swallow:
 - Oral glucose 15–20 g (Fast-acting carbohydrates such as glucose tablets, candy, or juice)
 - Chocolate is not recommended as it contains fat which shown to slow the absorption of quick acting carbohydrate.
 - ⇒ Repeat capillary blood glucose measurement 10-15 minutes later. If it is still less than 4.0mmol/L, repeat step 1 (no more than 3 treatments in total).
 - ⇒ If blood glucose remains less than 4.0mmol/L after 30-45 minutes or 3 cycles, Consider: 150-200ml of 10% I.V glucose over 15 minutes
 - ⇒ Once blood glucose is above 4.0mmol/L and the patient has recovered, give a long acting carbohydrate (e.g. Two biscuits, One slice of bread/toast, 200-300ml glass of milk, Normal meal if due.
- For patient who are unable to swallow (e.g. Glasgow Coma Scale Score < 13):
 - ⇒ If intravenous access can be obtained.
 - I.V glucose:
 - 10% or 20% glucose solutions are preferred options:
 - ⇒ give 75-**100ml** of **20%** glucose **over 15 minutes**. Repeat capillary blood glucose measurement 10 minutes later. If it is still less than 4.0mmol/L, repeat.
 - ⇒ give 150-200ml of 10% glucose over 15 minutes. Repeat capillary blood glucose measurement 10 minutes later. If it is still less than 4.0mmol/L, repeat
 - 50% intravenous dextrose is not recommended by Joint British
 Diabetes Societies (JBDS): (hyperosmolarity →↑risk of extravasation
 injury, venous endothelium destruction and phlebitis).
 - ⇒ if no intravenous access can be obtained → Glucagon (1 mg intramuscularly)
 - Glucagon acts on the liver by <u>Activates adenylate cyclase</u> → ↑
 glycogenolysis and gluconeogenesis → rapid correction of hypoglycaemia

Hypoglycaemic symptoms with normal blood glucose level

- Adults who have poor glycaemic control may start to experience symptoms of hypoglycaemia above 4.0mmol/L.
- adults who are experiencing hypoglycaemia symptoms but have a blood glucose level greater than 4.0mmol/L – treat with a small carbohydrate snack only e.g. 1 medium banana, a slice of bread or normal meal if due. (diabetologists-abcd.org.uk)

MRCPUK-part-1-September 2011 exam: An 18-year-old girl is admitted with hypoglycaemia (RBS: 1.9 mmol). her father who has type 2 DM describes a number of similar episodes. Insulin15 mg/ml (6-10 mg/ml)Proinsulin22% (22-24%) C-peptide 0.15 nmol/l (0.2-0.4 nmol/l).What is the most likely diagnosis? Insulin abuse (The raised insulin with low c-peptide level points to a diagnosis of insulin abuse. C-peptide levels would be raised in a patient following sulfonylurea abuse)

Hypoglycaemic episodes after regular exercise in patient who takes BD mixed insulin:

 the most appropriate next step in his management is → transfer to a basal bolus regime where he can alter his short acting insulin dose just prior to planning exercise.

Diabetes mellitus: early morning hyperglycemia

Overview

- The most common causes of morning hyperglycemia are nocturnal growth hormone secretion and hypoinsulinaemia.
- There is no evidence to support the existence of Somogyi effect (nocturnal hypoglycemia leading to a surge of counterregulatory hormones, leading to hyperglycemia in the morning). The opposite is typically found, ie, patients with morning hyperglycemia typically have high, not low, blood glucose concentrations at night.

Dawn phenomenon

- Definition: A physiological increase of growth hormone (GH) levels in the early morning hours stimulates hepatic gluconeogenesis and leads to early-morning hyperglycemia
- Diagnosis: measurement of nocturnal blood glucose → normal nocturnal glycemia, with early-morning hyperglycemia
- Treatment: Long-acting insulin dose may be given later or increased under careful glycemic control.

Hypoglycaemia unawareness (HU)

Definition

 Hypoglycemia unawareness (HU) is defined as onset of neuroglycopenia before the appearance of autonomic warning symptoms.

Incidence

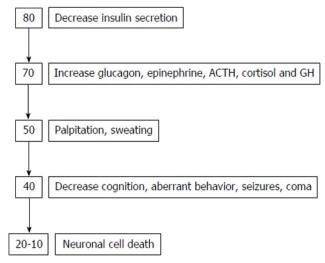
• Occurs in approximately 40% of people with type 1 diabetes mellitus (T1DM) and with less frequency in T2DM.

Mechanism

- Recurrent hypoglycaemia → hypoglycemia-associated autonomic failure (HAAF) → failure
 of counter-regulatory hormones → inability to recognise impeding hypoglycaemia by
 symptoms.
- Impaired awareness of the symptoms of plasma glucose levels below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia.
- more common in patients with <u>intensively controlled</u> <u>diabetes</u> of long duration, leading to recurrent hypoglycaemia.
- Alcohol inhibits gluconeogenesis, decreases peripheral hypoglycaemic responses and impairs perception of symptoms of hypoglycaemia.

Symptoms and signs associated with progressive hypoglycemia

Blood glucose (mg/dL)



Treatment

- Optimizing insulin treatment, flexible insulin therapy using basal–bolus regimens → Avoidance of hypoglycemia
- avoid hypoglycaemia in adults with type 1 by offering insulin pump and real-time continuous glucose monitoring.
- In recurrent severe hypoglycaemia that has not responded to other treatments refer to islet cell transplantation.
- NICE advise to avoid relaxing individualised blood glucose targets to address impaired hypoglycaemia awareness → use the recommended targets
- The patient demonstrating hypoglycemia unawareness is required to stop driving for 3 months after a second episode of hypoglycaemia.

Hyperosmolar hyperglycaemic state (HHS)

Pathophysiology

- Severe hyperglycemia → ↑ serum osmolality → osmotic diuresis → severe dehydration
- In general, there is enough insulin in patients with type 2 diabetes to suppress
 ketogenesis, but insufficient to prevent hyperglycaemia and the hepatic resistance to
 glucagon.

Overview

- Occurs most commonly in elderly people with type 2 diabetes
- Infection is the commonest precipitating factor (80%).
- Mortality is higher than DKA (5% to 15%).

Features

- · Osmotic features : Polyuria, polydipsia,
- Dehydration: dry mucous membranes, poor skin turgor, hypotension.
- Acute cognitive impairment (lethargy, disorientation, stupor) is common

Diagnostic criteria

- Hypovolaemia
- Hyperglycemia (≥ 30 mmol/L)
- ↑ Serum osmolality (> 320 mOsm/kg)
- Normal serum pH and ketones (pH >7.3, bicarbonate >15mmolL and no significant ketonenaemia <3mmol/L)

Management

Fluids

- ⇒ Fluid losses in HHS are estimated to be between 100 220 ml/kg (e.g. 10-22 litres in an individual weighing 100 kg).
- ⇒ The fluid of choice is 0.9% sodium chloride (NaCL)
- ⇒ Only switch to 0.45% (NaCL) if the osmolality is not declining despite adequate positive fluid balance. An initial rise in sodium is expected and is not itself an indication for hypotonic fluids.
- ⇒ Fluid replacement alone with 0.9% sodium chloride solution will result in falling blood glucose.
- ⇒ IV fluid replacement should aim to achieve a positive balance of 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within the next 12 hours.

Insulin

Low dose IV insulin (0.05 units/kg/hr) should only be commenced once the blood glucose is no longer falling with IV fluids alone OR immediately if there is significant ketonaemia (3β-hydroxy butyrate greater than 1 mmol/L or urine ketones greater than 2+)(e.g. mixed DKA / HHS picture).

Potassium

- ⇒ Patients with HHS are potassium deplete, decreased intracellular K+ (normal or increased serum K+).
- less common problem in HHS than DKA but monitoring and replacement are essential
- ⇒ Potassium should be replaced or omitted as required
- ⇒ If potassium level in first 24 hr (mmol/L) → No potassium replacement
- \Rightarrow If K : 3.5 5.5 \rightarrow 40 mmol/L
- ⇒ If K below 3.5 → senior review as additional potassium required
- Prophylactic anticoagulation: low molecular weight heparin (LMWH)

Targets

- The fall in blood glucose should be no more than 5 mmol/L/hr
- The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- Rapid changes of serum osmolarity are dangerous and can result in cardiovascular collapse and central pontine myelinolysis (CPM).
- Measure or calculate osmolality (2Na+ + glucose + urea) frequently to monitor treatment response

Complication

- Thrombotic events such as myocardial infarction, stroke or peripheral arterial thrombosis.
- Cerebral oedema, seizures secondary to rapid reduction in serum osmolality.
- Rapid correction of hyponatraemia, may lead to cerebral pontine myelinolysis

Diabetes mellitus: hypertension management

Antihypertensive therapy is the single intervention most likely to reduce the overall risk of both microvascular and macrovascular events.

- Lipid lowering therapy → prevent macrovascular events, but has no effect on microvascular events.
- Lowering HbA_{1c} only prevent → microvascular events.

First-line antihypertensive drug

- For most diabetics regardless the age → ACE inhibitor.
- For African or Caribbean family origin: ACE inhibitor plus either a diuretic or a generic calcium-channel blocker.
- For a woman for whom, there is a possibility of becoming pregnant → calcium-channel
- Because ACE-inhibitors have a renoprotective effect in diabetes they are the first-line antihypertensives recommended
- If an ACE inhibitor or ARB cannot be used, alternative first-line agents include calcium channel blockers and diuretics. However, in patients with severely increased albuminuria, nondihydropyridine agents (eg, diltiazem, verapamil) are generally preferred over dihydropyridine drugs (eg, amlodipine, felodipine), since nondihydropyridine calcium channel blockers can reduce albuminuria.
- The routine use of beta-blockers in uncomplicated hypertension should be avoided, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.

Targets: NICE recommend the following blood pressure (BP) targets for type 2 diabetics:

- If end-organ damage (e.g. renal disease, retinopathy) < 130/80 mmHg
- If NO end-organ damage < 140/80 mmHg

ACE inhibitors are first-line for hypertension in diabetics, irrespective of the patients age

Post prandial pain in diabetics

Macrovascular atherosclerosis in diabetes → Post prandial pain

- Diabetes, especially Type 2 diabetes, is associated with macrovascular disease.
- Smoking is a further risk factor for macrovascular atherosclerosis.
- After a meal splanchnic blood flow is increased. If the mesenteric artery is occluded the lack of blood flow to the bowel will produce ischaemic type pain.

Diabetic retinopathy

Definition

 Diabetic retinopathy is the retinal consequence of chronic progressive diabetic microvascular leakage and occlusion.

Epidemiology

- The most common cause of visual impairment and blindness in adults aged 25-65 yearsold.
- About 80% of patients with type I diabetes will have retinopathy 10 years after
 presentation. By contrast, in type II diabetes, where the time of onset is uncertain, up
 to 25% of patients will have retinopathy at the time of diagnosis.
- Features of retinopathy usually do not appear in patients with type 1 diabetes for up to 5 years following diagnosis.

Causes of rapid worsening of diabetic retinopathy

- Pregnancy
- Rapid improvement in blood glucose
 - ⇒ suddenly dropped glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy.
- The risk of diabetic retinopathy significantly increased in smokers with type 1 diabetes while significantly decreased in smokers with type 2 diabetes (a meta-analysis published in 2018).

Pathogenesis

- Hyperglycaemia → ↑ retinal blood flow & abnormal metabolism in the retinal vessel walls → damage to endothelial cells & pericytes
 - \Rightarrow Endothelial dysfunction $\rightarrow \uparrow$ vascular permeability \rightarrow exudates (seen on fundoscopy).
 - ⇒ **Pericyte dysfunction** → predisposes to the formation of **microaneurysms**.
 - ⇒ Retinal ischaemia → production of growth factors → Neovasculization

Which factor has been shown to have an important role in regulating retinal capillary blood flow?

- Contractile action of pericytes.
- DM →
 \psi retinal pericytes (normally contractile action of pericytes regulates retinal capillary blood flow) → disordered blood flow regulation →
 \cap retinal blood flow →
 \cap shear stress on the vessel walls → retinopathy.

The most likely cause of blurred vision in a newly diagnosed diabetic who was previously fit and well is \rightarrow Osmotic changes in the lens.

Features

- Asymptomatic until very late stages of disease
- Visual impairment
- Progression to blindness

Classification

The earliest sign of diabetic retinopathy is the presence of microaneurysms on fluorescein angiography.

Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

Traditional classification	New classification
Background retinopathy	Mild NPDR 1 or more microaneurysm Moderate NPDR microaneurysms blot haemorrhages hard exudates cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR Severe NPDR blot haemorrhages and microaneurysms in 4 quadrants venous beading in at least 2 quadrants IRMA in at least 1 quadrant

Non-Proliferative Diabetic Retinopathy (NPDR)

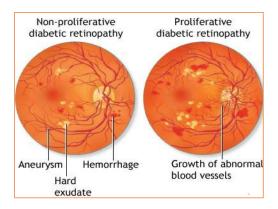
- Subtypes
 - **⇒** Mild NPDR
 - 1 or more microaneurysm
 - - Microaneurysms
 - blot haemorrhages
 - hard exudates
 - cotton wool spots, venous beading/looping and intra-retinal microvascular abnormalities (IRMA) less severe than in severe NPDR
 - **⇒** Severe NPDR
 - blot haemorrhages and microaneurysms in 4 quadrants
 - venous beading in at least 2 quadrants
 - IRMA in at least 1 quadrant
- Management
 - ⇒ regular observation
 - ⇒ if severe/very severe consider panretinal laser photocoagulation

Proliferative retinopathy

- Features
 - ⇒ More common in Type I DM, 50% blind in 5 years
 - ⇒ Normal visual acuity is seen in proliferative retinopathy
 - ⇒ Retinal neovascularisation (new vessels)- may lead to vitrous haemorrhage
- Management
 - ⇒ Urgent referral to an ophthalmologist (seen within one week)
 - ⇒ laser photocoagulation: 90% effective in preventing loss of vision in type 1 diabetes.
 - ⇒ Intravitreal anti-vascular endothelial growth factor (VEGF) injection
 - ⇒ If severe or vitreous haemorrhage: vitreoretinal surgery.

Maculopathy

- More common in Type II DM
- May occur in all stages of NPDR and PDR
- Macular oedema is a common form of maculopathy: Occurs when there is abnormal leakage and accumulation of fluid in the macula from damaged blood vessels in the nearby retina
- Mechanism: Retinal vessel microangiopathy → blood leaks → retinal hemorrhages → retinal infiltration with lipids and fluid → macular edema
- Features
 - ⇒ Macular oedema, Hard **exudates** and macular ischemia.
 - ⇒ The exudates can be arranged in a ring (circinate exudates) surrounding a point of capillary leakage.
- Diagnosis: Can be shown on fluorescein angiography
- Management
 - ⇒ check visual acuity
 - ⇒ responds to laser treatment at the point of leakage.
 - ⇒ If there is a change in visual acuity then intravitreal vascular endothelial growth factor (VEGF) inhibitors.



Cotton wool spots (CWS) is a pre-proliferative feature: represent infarcts of the nerve fibre layer of the retina.

Diabetic Eye Screening Programme (NHS-2015)

- Screening for diabetic retinopathy is offered to all people <u>aged 12 and over</u> with type 1 or type 2 diabetes.
- Intervals between screening tests
 - ⇒ For diabetics at low risk of sight loss: one year to two years.
 - ⇒ For those at high risk of sight loss: one-year

Treatment

- · Glycaemic control
 - ⇒ Achievement of target HbA1c of 47.54 mmol/mol (6.5%) would be associated with significantly reduced progression of retinopathy.
 - Should be done gently and gradually (over several weeks) because suddenly drop glucose levels → retinal artery vasoconstriction → rapid deterioration of retinopathy.
- Hypertensive control has been shown to be more effective than glycaemic control at reducing progression.
- Indications for emergency referral to ophthalmologist:
 - ⇒ sudden loss of vision
 - □ rubeosis iridis
 - ⇒ pre-retinal or vitreous haemorrhage
 - ⇒ retinal detachment.
- Indication for urgent referral to the ophthalmologist (seen within one week)
 - ➡ Hard exudates in the macular region (evidence of clinically significant macular oedema)
 - ⇒ proliferative retinopathy
 - ⇒ Vitreous haemorrhage

Prognosis

- The percentage of irreversible loss of vision within 5 years if not treated:
 - ⇒ 3% in those with background retinopathy
 - ⇒ 20% for those with exudative
 - ⇒ 30% for those with pre-proliferative.
 - ⇒ 50% for those with proliferative retinopathy.

Asymmetric diabetic retinopathy

Asymmetric DM Retinopathy → suspect ocular ischemia (carotid artery disease)

 Asymmetric diabetic retinopathy should always raise the suspicion that there is some other cause of ocular ischaemia on the worst-affected side, such as unilateral or asymmetrical carotid artery disease → do Carotid Doppler.

Hypertensive retinopathy



The presence of flame and blot haemorrhages, cotton wool spots and blurring of the optic disc margins are typical of the retinal changes that are seen in advanced hypertensive retinopathy. Whilst some of these findings are also observed in diabetic eye disease (e.g. dot and blot haemorrhages, cotton wool spots), the absence of other features (e.g. hard exudates, venous beading) should alert the clinician to other possible diagnoses.

Diabetic retinopathy during pregnancy

Diabetic retinopathy may rapidly deteriorate during pregnancy; therefore needs dilated fundoscopy or photography every trimester (3 monthly).

 Because of the increased risk of progression of the disease in pregnancy, conception should be delayed till the ocular disease is treated and stabilized and good diabetic control.

Diabetic neuropathy

Mechanism of neuropathy in diabetes (Nerve ischemia)

Diabetes damages small blood vessels, which supply the nerve leads to nerve ischaemia.

Overview

- Chronic hyperglycaemia damages small blood vessels, which supply the nerve leads to nerve ischaemia.
- Distal symmetric polyneuropathy is the most common form.
- Sensory nerves are affected more than motor so often reflexes remain intact.
- Diabetic peripheral neuropathy usually goes in parallel with retinopathy and nephropathy.
- It is also slowly progressive and affects mainly the spinothalamic pathway.
- The most distal portion of the longest nerves is affected first.

Risk factors

- poorly controlled hyperglycaemia
- prolonged duration of diabetes (e.g., >10 years)
- Older age (e.g., >70 years)
- Tall stature (longer fibres are more vulnerable to injury).
- Hypertension
- Smoking
- Dyslipidaemia with elevated triglycerides
- co-existence of multiple CVD risk factors (type 2 diabetes)

Features

- Asymptomatic (Up to 50%), but the physical examination reveals mild to moderately severe
 progressive symmetric loss of sensation in the distal lower extremities (stocking glove
 sensory loss)
- Pain is the most common symptom induced by the involvement of small fibres

- Loss of sensation → painless injuries over pressure points, most commonly on the foot, over the metatarsal heads.
- Autonomic features

Symptoms and signs of distal symmetric polyneuropathy (DSPN)

	Large, myelinated nerve fibers	Small, myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms	Numbness, tingling, poor balance	Pain: burning, electric shocks, stabbing
Examination	Ankle reflexes: reduced/absent	Thermal (cold/hot) discrimination:
(clinically	Vibration perception: reduced/absent	reduced/absent
diagnostic)	10 g monofilament (light pressure):	Pinprick sensation: reduced/absent
	reduced/absent	
	Proprioception: reduced/absent	

Large fiber involvement in neuropathy results in **reduced proprioception**, light pressure and **vibration sensation** and is the **earliest <u>clinically identifiable</u>** feature of peripheral sensory motor neuropathy.

Short fiber neuropathy is a **later manifestation** of diabetic peripheral neuropathy, with symptoms including **hyperparesthesia** and **superficial pain**. Examination findings indicative of short fiber neuropathy include **impaired thermosensation**, **reduced sweating** and a **cold foot**

Treatment: First-line: duloxetine, amitriptyline, gabapentin or pregabalin

- Duloxetine
 - Action: serotonin-norepinephrine reuptake inhibitor (SNRI)
 - ⇒ Duloxetine is preferred to amitriptyline because it is associated with a lower risk of urinary retention.
 - ⇒ Contraindications:
 - history of glaucoma
 - patients already taking a serotonergic agent, such as tramadol, because of the associated risk of serotonin syndrome.
- Amitriptyline
 - ⇒ recommended by NICE as second line if duloxetine is unsuitable.
 - ⇒ Contraindications:
 - glaucoma and left bundle branch block
- Pregabalin or gabapentin
 - ⇒ Action: voltage-gated calcium channel modulator
 - ⇒ considered as second or third line monotherapy or in combination.
 - ⇒ If there is renal impairment, pregabalin is preferable over gabapentin.
- If the first-line drug treatment does not work try one of the other 3 drugs

Pharmacotherapy for painful diabetic neuropathy: Relevant comorbidities for drug selection

Drug class	Comorbidities favoring use	Comorbidities favoring avoidance
Serotonin-norepinephrine	 Depression 	Restless legs syndrome
reuptake inhibitors (SNRIs)	 Anxiety 	Sexual dysfunction (for
Duloxetine		venlafaxine)
Venlafaxine		Angle-closure glaucoma
Tricyclic antidepressants	Depression	Cardiac disease
(TCAs)	 Anxiety 	Prolonged QTc
Amitriptyline	 Insomnia 	Orthostatic hypotension
 Nortriptyline 		 Sexual dysfunction
 Desipramine 		 Urinary retention
		Angle-closure glaucoma
Gabapentinoid anticonvulsants	Restless legs syndrome	Substance abuse
 Pregabalin 	 Essential tremor 	Peripheral edema
 Gabapentin 	 Insomnia 	Chronic obstructive pulmonary
		disease

<u>Peripheral neuropathy</u> with H/O <u>glaucoma</u> and on <u>tramadol</u> for chronic back pain, what is the best treatment?

Pregabalin

Acute painful neuropathy of rapid improvement of blood glucose control

- rapid improvement of blood glucose control → Acute painful neuropathy (self-limiting)
 → Simple analgesics (paracetamol, aspirin) and local measures (bed cradles) are recommended as a first step
- Duloxetine is the standard first line therapy for neuropathy
- Amitriptyline is an alternative option to duloxetine if it is contraindicated; (e.g. presence of glaucoma)
- Pregabalin is recommended either as a second line agent or in combination with amitriptyline.

MRCPUK-part-1-September 2009 exam: H/O type 2 DM and benign prostatic hypertrophy (BPH) presents with burning pain in his feet. He tried duloxetine but no benefit. What is the most suitable initial management?

- Pregabalin
- Amitriptyline is first choice but given H/O BPH, it is better to avoid amitriptyline due to the risk of urinary retention.

Diabetic autonomic neuropathy

Features

Urogenital system	Erectile dysfunction (most common)
	Bladder dysfunction: urinary retention, incomplete bladder emptying,
	bladder distention, overflow incontinence, poor urinary stream
Cardiovascular	Silent myocardial infarction
system	Decreased heart variability or fixed rhythm
	Orthostatic hypotension
	Persistent sinus tachycardia
	Ventricular arrhythmia
Gastrointestinal	Gastroparesis
system	 ⇒ Delayed gastric emptying due to nonmechanical obstruction ⇒ Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery ⇒ Manifested with nausea, abdominal bloating, early satiety
	 ⇒ Increased risk of postprandial hypoglycemia ⇒ Treatment involves prokinetic agents, e.g., metoclopramide (first-line), erythromycin, domperidone.
	Diarrhea, constipation, incontinence
Other	Sweat gland dysfunction associated with heat intolerance
manifestations	Pupillary dysfunction
	Risk of hypoglycemia due to absence of hormonal counter-regulation
	(secretion of cortisol, glucagon, and catecholamines)

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomiting \rightarrow Think about a diagnosis of gastroparesis.

Diabetic amyotrophy

Leg pain, weakness and reduced knee reflexes with an impaired fasting glucose concentration suggests a diagnosis of diabetic amyotrophy →should be confirmed with OGTT.

Definition

 Diabetic amyotrophy is a type of diabetic neuropathy which affects the lumbosacral plexus, nerve roots and peripheral nerves, therefore known as proximal diabetic neuropathy and diabetic lumbosacral plexopathy. It is a mixed motor and sensory proximal neuropathy that can cause severe pain.

Epidemiology

- Relatively uncommon, affect 1% of patients
- Typically occurs in patients with type 2 diabetes mellitus that has been recently diagnosed or has been under fairly good control.

Pathophysiology

 The most likely mechanism is ischemic injury from microvasculitis leading to axonal degeneration (e.g. occlusion of the vasa nervorum of the proximal lumbar plexus and/or femoral nerve).

Differences from other types of diabetic neuropathy

- Patients usually have <u>not had diabetes for a long time</u>, and glycaemic dysregulation is often not severe.
 - ⇒ A diagnosis of diabetic amyotrophy leads to the discovery of underlying diabetes mellitus in one quarter to one third of cases.
 - ⇒ Long-term diabetic complications such as diabetic retinopathy and nephropathy are often absent at the time of diagnosis.

Features

- Pain is usually the first symptom, often in the thigh, hips or buttocks
- Often asymmetrical (although it can be bilateral).
- Wasting and weakness of proximal muscles (e.g. difficulty getting out of a chair)
- Weight loss
- Loss of knee reflexes
- There is often little sensory loss.
- Autonomic failure

Investigations

- EMG shows multifocal denervation in paraspinous & leg muscles.
- MRI is useful to rule out other causes of neurologic impairment, such as structural lesions
 of the lumbosacral plexus, brachial plexus, or spinal cord.

Prognosis

- Often self-improvement with time
- Most patients will not recover completely.

Treatment

- No treatments are proven to be effective.
- Neuropathic pain treatments include amitriptyline, gabapentin, pregabalin, or duloxetine.
- May improve with good control (the mainstay of treatment is supportive care and transference to insulin therapy).

Diabetic foot

Epidemiology

2% of patients with diabetes in the community develop new foot ulcers each year

Pathophysiology

- It occurs secondary to two main factors:
 - ⇒ **neuropathy:** resulting in loss of protective sensation (e.g. not noticing a stone in the shoe), Charcot's arthropathy, dry skin
 - peripheral arterial disease: diabetes is a risk factor for both macro and microvascular ischaemia

Presentations

- Neuropathy: loss of sensation
- Ischaemia: absent foot pulses, reduced ankle-brachial pressure index (ABPI), intermittent claudication
- Complications: calluses, ulceration, Charcot's arthropathy, cellulitis, osteomyelitis, gangrene

Screening

- All diabetic patients should be screened for diabetic foot at least annually.
- screening for ischaemia: done by palpating for both the dorsalis pedis pulse and posterior tibial artery pulse
- screening for neuropathy: a 10 g monofilament is used on various parts of the sole of the foot.

Differential diagnosis

- · Venous stasis ulcers
 - ⇒ **Mechanism:** Venous reflux → congestion and dilated veins, which impair the transport of fresh blood to the area.
 - ⇒ Sites: Typically present in the area around the ankle
 - □ Treatment:
 - Multi-layer bandaging is most useful in reducing lower limb oedema and improving the chances of healing of venous ulcers.
 - An ankle brachial pressure index (ABPI) measurement is essential before beginning bandaging, as if there is significant arterial insufficiency, blood supply to the lower limb may be threatened.

Features

Neuropathic foot	Ischaemic foot
often warm	Cold foot
Painless or abnormal neuropathic pain.	causes rest pain
bounding pulses	nearly pulseless foot
ulceration tends to occur on the plantar surface	Ulceration tends to be painful and often presents in the heal area
It can be high arched, with toe clawing.	there is often gravity-dependent reddening of the foot, which disappears on elevation of the foot.

In about one third of patients with diabetic foot, the underlying cause is both ischemic and neuropathic.



This is a typical **neuropathic ulcer**, with callus forming the edge and a clean base.

Diabetic neuropathic arthropathy (Charcot foot)

In patients with long-standing diabetes and peripheral neuropathy, a **red**, **hot swollen foot** should raise suspicion of Charcot neuroarthropathy after exclude infection.

Definition

Disrupted and damaged joint (mid-foot collapse) secondary to a loss of sensation.

Causes

• Diabetes mellitus (The most common cause)

Pathophysiology

- Multifactorial, due to a combination of mechanical, neuropathic and vascular
 - ⇒ Peripheral neuropathy (lack of pain sensation) → ↑ stress injuries to foot joints (commonly the midfoot) → Charcot process.
 - ⇒ Autonomic neuropathy →↑ blood flow to the joint → ↑ osteoclast activity and bone turnover "washing out" of bone substance → ↑foot susceptibility to minor trauma → destructive changes → Charcot's
- The commonest affected joints are tarso-metatarsal joint and metatarsophalangeal joint.

Features

- The foot and ankle are typically <u>swollen</u>, <u>red</u> and <u>warm</u>
- Midfoot arch collapse can lead to bony prominences on the plantar aspect with later pressure ulceration
- Typically, less painful than would be expected given the degree of joint disruption due to the sensory neuropathy. However, 75% of patients report some degree of pain

Diagnosis

- Infection such as osteomyelitis is important to exclude.
 - ⇒ Normal C-reactive protein and white blood cell count → make osteomyelitis unlikely
 - Although not widely available, an <u>indium-labelled white cell scan</u> is the best way to differentiate between infective causes of this clinical presentation and Charcot's arthropathy.

- X-ray: plain radiographs can be normal in the early stages. later on, they show joint destruction, osteolysis, joint reorganisation and subluxation.
- . MRI: in acute Charcot's arthropathy shows midfoot subchondral bone marrow edema

Management

- Immobilisation in a plaster cast for 3-6 months is the treatment of choice.
- Bisphosphonates: bisphosphonates → reduction in bone reabsorption → accelerate healing.
- Surgery: reserved for severe deformities

Necrobiosis lipoidica diabeticorum

Definition

 A disorder of collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition.

Causes

- Occurs in patients with type 1 diabetes.
- It is usually related to diabetes, but can also occur in patients with rheumatoid arthritis
- May precede symptoms and signs of diabetes by several months.

Epidemiology

- More common in females
- Presents in young adults or in early middle life.

Features

- Typically, painless.
- Beginning as a patch of erythema that spreads across the shin, begins to yellow and can then ulcerate.

Diagnosis

 Biopsy reveals granuloma formation with infiltration of lymphocytes, plasma cells and eosinophils.

Treatment

- Topical steroids is the most appropriate treatment to the non-atrophied areas. the areas of already atrophied skin respond poorly to steroid therapy.
- · Support bandaging



Diabetes mellitus: DVLA

Patients on insulin may now hold a HGV licence if they meet strict DVLA criteria

If a patient has two or more episodes of severe hypoglycaemia (i.e. patient needs help to correct the hypoglycaemic episode) then they need to inform the DVLA and not drive.

Type 1 vehicles (cars, motorcycles)

- If on insulin then patient can drive a car as long as they:
 - ⇒ have hypoglycaemic awareness,
 - ⇒ not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
 - ⇒ no relevant visual impairment.
 - ⇒ Drivers are normally contacted by DVLA
- If on diet controlled alone, tablets or exenatide no need to notify DVLA.

Type 2 vehicles (lorries, HGV)

- HGV drivers can retain their license even if taking insulin, providing they are able to meet a set of criteria.
- Criteria regarding driving for patient on insulin (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):

- having no episodes of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- evidence of good glycemic control demonstrated by review of 3months of BM readings on insulin
- 3) close BM monitoring (at least BD)
- 4) full hypoglycaemia awareness
- 5) the ability to manage hypoglycaemia independently
- 6) no other complications of diabetes (e.g. visual field impairments.)

Hypoglycaemia (DVLA regulations)

- Group 1 drivers who have had more than one episode of severe hypoglycaemia (requiring the assistance of another person) while awake in the last 12 months
 - ⇒ Must not drive and must notify the DVLA.
 - ⇒ DVLA will then carry out medical enquiries before a licensing decision is made.
- Group 2 drivers who have had more than one episode of severe hypoglycaemia
 - ⇒ Must not drive and must notify the DVLA following all episodes of severe hypoglycaemia including asleep episodes.
- Severe hypoglycaemia whilst driving
 - ⇒ All Group 1 and Group 2 drivers must not drive and must notify the DVLA.

Impaired awareness of hypoglycaemia – 'hypoglycaemia unawareness'

Group 1 (Car and motorcycle)	Group 2 (Bus and lorry)
 Must not drive and must notify the DVLA. Driving may resume <u>after a clinical report</u> by a GP or consultant diabetes specialist <u>confirms that hypoglycaemia awareness has been regained.</u> 	 Must not drive and must notify the DVLA. The licence will be refused or revoked.

- Who will inform the DVLA?
 - ⇒ the patient should be advised to inform the DVLA themselves rather than breaking patient confidentiality.
 - ⇒ if the patient repeatedly fails to follow this advice, then **the doctor should inform the DVLA** after telling the patient that he or she is doing so.
- What advice should be given to a patient on insulin therapy, who developed hypoglycaemia requiring the assistance of another person in the preceding twelve months, with respect to his driving?—Discontinue driving for 1 year

A guide for drivers with insulin treated diabetes who wish to apply for Group 2 (bus and lorry)

- No hypoglycaemic event requiring the help of another person in the last 12 months.
- must have full awareness of the symptoms of hypoglycaemia.
- must be able to show an understanding of the risks of hypoglycaemia.
- must check blood sugar levels at least twice daily, even on non-driving days and no more
 than 2 hours before the start of the first journey and every 2 hours while driving. This must
 be done using a blood glucose (sugar) meter with a memory function to measure and
 record blood glucose levels.

- must attend an examination every 12 months with an independent consultant specialising in the treatment of diabetes.
- must have at least 3 continuous months of readings available on the memory of the blood glucose meter(s) for the consultant/GP to inspect.

Drivers with insulin treated diabetes are advised by DVLA to:

- should check glucose less than 2 hours before the start of the first journey and every 2 hours after driving has started.
- A maximum of 2 hours should pass between the pre-driving glucose check and the first glucose check after driving has started.
- In each case if glucose is 5.0mmol/L or less, eat a snack. If it is less than 4.0mmol/L or feel hypoglycaemic do not drive.

DVLA advice on developing hypoglycaemia at times relevant to driving

- In each case if your glucose is 5.0mmol/L or less, eat a snack.
- If it is less than 4.0mmol/L or you feel hypoglycaemic do not drive.
- If hypoglycaemia develops while driving stop the vehicle safely as soon as possible.
- You should switch off the engine, remove the keys from the ignition and move from the
 driver's seat.
- You should not start driving again until 45 minutes after finger prick glucose has returned to normal (at least 5.0mmol/L). It takes up to 45 minutes for the brain to recover fully.
- Your finger prick glucose level must be at least 5.0mmol/L before returning to driving.

Jobs that not allowed to subjects with insulin dependent diabetes

- Armed forces
- Working offshore or aboard ships
- Air pilot
- Police, Fire or driving in the post office (Traffic police driver)
- Driving emergency vehicles
- Offshore work

If a patient has two or more episodes of severe hypoglycaemia (needs help to correct the hypoglycaemic episode) then they need to <u>inform the DVLA and not drive.</u> (needs to surrender their driving licence)

Insulinoma

Insulinoma is diagnosed with supervised prolonged fasting

Definition

• Insulinoma is a neuroendocrine tumor arise from beta cells of the pancreas

Overview

- Most common pancreatic endocrine tumour
- incidence of 4 cases per million/year
- · commoner in women
- 10% malignant. 90% are benign.
- 10% have multiple tumours. ~ 90% occur as solitary tumors

- 10% may be associated with the MEN-1 syndrome (50% of patients with multiple tumours, have MEN-1)
- 90% are less than 2 cm in size.
- < 1% occur at ectopic sites (e.g., spleen).

Features

Whipple triad is required before further investigations for insulinoma:

- 1. hypoglycemic symptoms,
- 2. low blood glucose level
- 3. resolution of symptoms after correcting the blood glucose levels.
- Features of hypoglycaemia: typically fasting hypoglycemia (early in morning or just before meal). e.g. hunger, diplopia, sweating, palpitations, memory loss, seizures.
- Rapid weight gain: Patients eat in an attempt to avoid hypoglycaemia

Diagnosis

- Insulin + C-peptide levels during a hypoglycaemic episode
 - ⇒ hypoglycemia with inappropriately high insulin levels (hyperinsulinism)
 - ⇒ high C-peptide
 - ⇒ raised proinsulin: insulin ratio
- Supervised, prolonged fasting (up to 72 hours)
 - ⇒ If the patient develops symptoms, then a plasma glucose is measured and if low, insulin and C-peptide is then collected and the fast terminated.
 - ⇒ Positive if serum glucose levels remain low (< 40 mg/dL) and insulin levels remain high even after fasting for 72 hours.
 - ⇒ After a 15 h fast, the cut-off normal limits for glucose are 2.5 mmol/l and 5 mU/l for insulin.
 - ⇒ By 24 h, fasting leads to a detection rate of 78% for insulinoma. If the fast is extended to 72 h, this detection rate increases to 98%.
- Sulphonylurea screen to exclude possible drug administration
- Images to localize the tumor. abdominal CT with contrast.

Elevated C-peptide and proinsulin levels may also be the result of sulfonylurea use! This can be ruled out by screening serum samples for sulfonylureas.

Management

- Surgery is treatment of choice
- If surgery is not possible (unfit, refusal, inoperable tumor) → inhibitors of insulin release
 - → **Diazoxide** (potassium channel activator)

Glucagonoma

Glucagon physiology

- Made by α cells of pancreas.
- Secreted in response to hypoglycemia.
- Inhibited by insulin, amylin, somatostatin, hyperglycemia.
- Functions (catabolic effects)
 - ⇒ ↑↑ gluconeogenesis from amino acid substrates.
 - ⇒ ↑↑ glycogenolysis
 - ⇒ ↑↑ lipolysis, ↑↑ amino acid oxidation , ↑↑ ketogenesis
 - ⇒ ↑↑ blood glucose
 - ⇒ ↑↑ catecholamine secretion
 - ⇒ Delays gastric emptying
 - ⇒ ↓↓ glycolysis
 - ⇒ ↓ pancreatic exocrine secretions.

Overview

- · A neuroendocrine tumor that secrete glucagon.
- Very rare, with an annual incidence of 1 in 20 million.
- Usually solitary, and the majority are located in the distal pancreas.
- · Frequently malignant.
- 50 80% are metastatic at presentation, so prognosis is poor.

Features

- Glucose intolerance, secondary diabetes mellitus
- · Weight loss due to protein catabolism
- · Chronic diarrhea
- Neuropsychiatric features
- Venous thrombo-embolism
- Necrolytic migratory erythema
 - ⇒ The most common symptoms (found in 75% of cases)
 - ⇒ Red, blistering rash, starts as an indurated erythema, within a few days blisters will cover the surface of the skin, which then crust and heal, leaving hyperpigmented skin.
 - ⇒ Located predominantly on the face, perineum, and lower extremities, with lesions developing in one area while others are resolving.

Glucagonoma → 6 Ds

- 1. Decreasing weight
- 2. Diabetes
- 3. Dermatitis
- 4. Diarrhea
- 5. DVT
- 6. Depression.

Diagnosis

- Measure plasma glucagon levels → Elevated
- Image: CT scan

Management

- Somatostatin analogs (eg, octreotide) → improves the skin rash and diarrhoea
- <u>Surgical</u> cure rate is only 5% because these tumours have often metastasized on presentation.

Monogenic diabetes: Maturity-onset diabetes of the young (MODY)

Definition

 Different forms of autosomal dominant inherited diabetes mellitus characterized by onset of diabetes at a young age (<25 years) and lack of autoantibodies.

Epidemiology

• It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

General features

- Subacute presentation (ketosis is not a feature at presentation).
- Mild to moderate hyperglycaemia (typically 7-14 mM).
- Absence of obesity → Absence of insulin resistance → low insulin requirement (e.g. less than 0.5 u/kg/day).
- · Strong family history of early onset diabetes.
- · Absence of autoimmune markers.

Diagnosis

- High index of suspicion (familial diabetes with autosomal dominant pattern of inheritance [≥3 generations], onset <25 years, nonobese, negative islet autoantibodies)
- Genetic testing: the most common mutations:
 - ⇒ hepatocyte nuclear factor-1-alpha (HNF1A) → MODY type 3
 - ⇒ glucokinase (GCK) → MODY type 2
 - ⇒ hepatocyte nuclear factor-4-alpha (HNF4A) → MODY type1

Subtypes

- MODY 3 (HNF1A-MODY)
 - ⇒ the **commonest** form of MODY, **60%** of cases
 - ⇒ due to a defect in the **HNF-1 alpha** gene (hepatic nuclear factor-1)
 - ⇒ characterised by:
 - ↑HDL cholesterol levels
 - Preserved insulin sensitivity
 - Low renal threshold for glucose (glycosuria)
 - ⇒ Sulphonylureas is the initial drug of choice
 - ⇒ MODY3 is particularly important to diagnose as many patients initially treated with insulin can in fact be managed with sulphonylurea.
- MODY 2 (GCK-MODY)
 - ⇒ **Prevalence: 20%** of cases (The second commonest MODY variant after MODY3)
 - ⇒ Mechanism: due to a defect in the glucokinase gene (GCK gene)
 - Glucokinase is found in the liver and in beta cells in the pancreas. acts as a sensor, recognizing when the level of glucose in the blood rises and helping stimulate the release of insulin from beta cells to control it. In the liver,

- glucokinase helps determine when excess glucose should be taken in and converted to glycogen.
- When this gene isn't working properly the body allows the level of blood glucose to be higher than it should be.
- ⇒ **Features:** Mild hyperglycaemia (slightly higher than normal, generally between 5.5-8mmol/l). Often picked up through routine testing (eg during pregnancy).
- ⇒ **Treatment:** 90% of MODY2 patients are controlled on **diet therapy alone**.
- ⇒ Prognosis: In contrast to all other subtypes, MODY II is not associated with an increased risk of microvascular disease and can be managed with diet alone, despite stable hyperglycemia and chronically elevated HbA1C levels.
- MODY type 1 (HNF4A -MODY)
 - ⇒ Defect in HNF-4 Alpha gene.
 - ⇒ The third commonest MODY (<10%)
 - ⇒ Beta cell defect: Reduced insulin secretory response to glucose
 - ⇒ Normal renal threshold for glucose
 - ⇒ Treatment : Sulfonylureas
- MODY 5 (HNF1B-MODY)
 - ⇒ Defect in HNF-1 beta gene.
 - ⇒ Rare
 - ⇒ Renal cysts
 - ⇒ Hypomagnesemia
 - ⇒ Treatment: insulin is usually necessary

Bilateral renal cysts + ↑ glucose → MODY related cyst formation

HNF4-alpha is associated with macrosomy, and with hypoglycaemia in the neonatal period. It is an uncommon form of MODY.

Latent autoimmune diabetes of adulthood (LADA)

Definition

• a variant of diabetes characterized by a late onset of type 1 (autoimmune) diabetes that is often mistaken for type 2 diabetes.

Epidemiology

constitutes approximately 10% of patients incorrectly labelled as type 2 diabetic.

Feature

- Features consistent with type 1 diabetes (eg: weight loss)
- In contrast to type 2 diabetes, patients are typically younger and without an increased body habitus.
- In contrast to type 1 diabetes, insulin is not usually required in the early stages of the disease, the progression of autoimmune -cell failure is slow.

Diagnosis

Glutamic Acid Decarboxylase (GAD) Autoantibodies test

Management

- early use of insulin may prolong beta-cell function
- a recent Cochrane review concluded that a <u>sulphonylurea should not be the first line</u> <u>treatment</u> since it may be <u>associated with a more rapid progression to insulin dependence</u>

Mitochondrial diabetes

Definition

• A rare variant of diabetes occurred due to mutation in the mitochondrial DNA.

Features

- Can present as type 1 or type 2 depending on the severity of insulinopenia.
- Strong familial clustering of diabetes. Although this is also seen in MODY, mitochondrial diabetes can be discriminated from MODY by:
 - ⇒ Presence of maternal transmission
 - ⇒ Bilateral hearing impairment (usually precede the development of diabetes) →do audiometry.

Diagnosis

- Mitochondrial diabetes is suspected in female patients with a strong familial clustering of diabetes, with predominantly maternal transmission of disease and the presence of sensorineural deafness.
- Genetic analysis → A3243G mutation in the tRNA gene

Treatment

- with type 2 DM presentation: due to an underlying mitochondrial mutation can be with sulfonylureas is the initial treatment of choice
- Metformin is contraindicated due to risk of development of lactic acidosis.
 - ⇒ A mitochondrial dysfunction in muscle is expected to lead to a higher lactate
 - ⇒ The A3243G mutation was originally detected in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome)

Mitochondrial diseases follow a maternal inheritance pattern

- · All children of affected females will inherit it.
- All children of affected males will not inherit the disease.

High glucose + sensorineural deafness → think of mitochondrial diabetes

Diabetes in pregnancy

Classification of diabetes in pregnancy

- Gestational diabetes (GDM) (developed during pregnancy): most common → 87.5% of all diabetic pregnancies.
- Pre-existing type 1 or type 2 diabetes

Epidemiology

• The prevalence of diabetes in pregnancy is 2–5% in the UK of both gestational diabetes and pre-existing diabetes.

Definition

- GDM refers to diagnosis of diabetes at 24 to 28 weeks of gestation.
- Diagnosis of diabetes in early pregnancy is more consistent with previously undiagnosed type 2 diabetes.

Gestational diabetes mellitus (GDM)

Risk factors for GDM

- BMI of > 30 kg/m
- previous macrosomic baby weighing 4.5 kg or above
- · previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for GDM

- Women who've previously had gestational diabetes:
 - ⇒ Oral glucose tolerance test (OGTT) should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal.
 - ⇒ NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs.
- Women with any of the other risk factors → OGTT at 24-28 weeks

Diagnosis: GDM is diagnosed if either:

- Fasting glucose is ≥ 5.6 mmol/l
- 2-hour glucose is ≥ 7.8 mmol/l
- If fasting blood glucose between 5.5 and 7.0 mmol/l then proceed to \rightarrow 75-g oral glucose tolerance test

The oral glucose tolerance test remains the investigation of choice for gestational diabetes

Complications

- Macrosomia (the commonest complications)
 - ⇒ defined by a birth weight > 4.5Kg
 - ⇒ affects up to 45% of babies
 - ⇒ shoulder dystocia is a common delivery problem occurring in up to 15 20% of cases.
- Neonatal hypoglycaemia
- Maternal complications are hypertension, preeclampsia, increased risk of developing diabetes mellitus and increased risk of cesarean delivery.

Management

- Advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- Aspirin should also be considered given the increased risk of pre-eclampsia.
- If the fasting plasma glucose level is < 7 mmol//l
 - ⇒ Trial of diet and exercise should be offered
 - ⇒ If glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
 - ⇒ If glucose targets are still not met insulin should be added to diet/exercise/metformin

- If at the time of diagnosis, the fasting glucose level is ≥ 7 mmol/l
 - ⇒ insulin should be started
- If the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios:
 - ⇒ insulin should be offered
- Fasting blood glucose should be checked 6 -13 weeks postpartum

Prognosis

the incidence of type 2 diabetes in women with a history of gestational diabetes is 16%

Pre-existing diabetes in pregnancy

Complications

 the risk of severe congenital malformation increased by two-fold in infants born to mother with pre-existing diabetes (pregestational diabetes)

Management

- Planning pregnancy
 - ⇒ Patients should achieve good diabetic control prior to planning for pregnancy.
 - ⇒ If this has not been achieved, then NICE advises contraception and to offer termination if pregnancy does occur due to increased risks in pregnancy.
 - ⇒ Control will reduce the risk of miscarriage, congenital malformation, stillbirth, and neonatal death.
- Stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- Folic acid 5 mg/day from pre-conception to 12 weeks gestation
- Aspirin 75mg/day from 12 weeks until the birth of the baby, to reduce the risk of preeclampsia
- Detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- Tight glycaemic control reduces complication rates
- Treat retinopathy as can worsen during pregnancy
 - It is advised, however, if the patient has not had <u>retinal screening within the last six months</u> to offer this <u>urgently</u> as there can be rapid development of diabetic retinopathy in pregnancy.
- Continuous glucose monitoring (CGM) improves glucose control

Patients with diabetes should have increased frequency of retinal screening during pregnancy due to increased risk of retinopathy

Targets for self-monitoring of pregnant women (pre-existing and gestational diabetes)

Time	Target
Fasting	5.3 mmol/l
1 hour after meals	7.8 mmol/l, or
2 hour after meals	6.4 mmol/l

Lipids and obesity problems

Obesity: overview

Classification

Classification	Body Mass Index (BMI) kg/m ²
Healthy weight	18.5-24.9
Overweight	25-29.9
Obesity I	30-34.9
Obesity II	35-39.9
Obesity III (Morbid obesity)	40 or more

Associated conditions

- Metabolic syndrome (hypertension, hyperglycaemia, hyperlipidaemia)
- · GI conditions: cholelithiasis, nonalcoholic fatty liver disease, GERD, colonic diverticulosis
- Respiratory: Obstructive sleep apnea (OSA), obesity hypoventilation syndrome (Pickwickian syndrome)
- Polycystic ovary syndrome
- · Mental health issues: e.g., depression, anxiety, eating disorders
- Gout

Hormonal alterations in obesity

- · Increased in obesity
 - ⇒ **Testosterone (female):** due to insulin resistance (PCOS) ↓ SHBG
 - ⇒ LH in (female): due to insulin resistance
 - ⇒ Insulin: due to ↑ insulin resistance
 - ⇒ **Renin:** due to ↑ Sympathetic tone
 - ⇒ **Aldosterone:** due to ↑ Adipokines, renin- angiotensin, leptin
 - ⇒ **Leptin**: due to increased adipose mass, Leptin resistance
- Decreased in obesity
 - ⇒ **Testosterone (male):** due to ↓ SHBG ↑ aromatase ↓GnRH
 - ⇒ LH/FSH (male): due to ↑ oestrogens/androgens
 - ⇒ Glucagon-like peptide-1 (GLP-1): due to ↑ FFA
 - ⇒ **25-OH vitamin D:** due to trapping in adipose tissue, ↓ sun exposure, ↓ 25OH vitamin D binding protein ↓ liver synthesis.
 - ⇒ Ghrelin

Obesity hormones

- · Leptin Lowers appetite
- · Ghrelin Gains appetite

Appetite regulation (ghrelin and leptin)

Leptin (the satiety hormone)

- Produced by adipose tissue.
- Acts on ventromedial area of hypothalamus (satiety center) to ↓↓ appetite.
- Obese people have \(\frac{1}{1} \) leptin due to \(\frac{1}{1} \) adipose tissue but are tolerant or resistant to leptin's anorexigenic effect.
- Mutation of leptin gene → severe obesity.
- Factors → ↓↓ leptin
 - ⇒ Starvation
 - ⇒ Sleep deprivation

Ghrelin (the hunger hormone)

- Produced by stomach
- Acts on hypothalamus to ↑↑ hunger, ↑↑gastric acid secretion and ↑↑GIT motility. Acts synergistically with GnRH to stimulate growth hormone release
- Regulate appetite → **stimulates hunger**
- Factors → ↑↑ghrelin
 - ⇒ Empty stomach (fasting)
 - ⇒ Sleep deprivation
 - ⇒ Prader-Willi syndrome
- Factors → ↓↓ghrelin
 - ⇒ Stretched stomach

Ghrelin makes you ghrow hunghry (the hunger hormone). Leptin keeps you thin (the satiety hormone).

Obesity: management (step-wise approach)

Lifestyle modifications

- Reduce fat intake
 - ⇒ The current UK recommendations: total fat intake should be restricted to less than 30% of dietary energy (the average daily energy consumption of a male is 2500 kcal and 2000 kcal for a female.)
- Physical activity: at least 30 minutes of moderate aerobic activity 5–7 times per week.

Pharmacological management: Anti-obesity drugs

- Indications:
 - ⇒ body mass index (BMI) ≥ 30 kg/m2 in whom at least three months of managed care involving supervised diet, exercise and behaviour modification fails.
 - ⇒ BMI ≥ 28 kg/m2 + risk factors (eg: diabetes mellitus, coronary heart disease, hypertension and obstructive sleep apnoea)
- Discontinuation: Anti-obesity drug treatment should be discontinued :
 - ⇒ If weight loss is less than 5% after the first 12 weeks.
 - ⇒ If the individual regains weight at any time whilst receiving drug treatment
- Contraindications:
 - ⇒ Combination drug therapy is contraindicated

⇒ Drugs should never be used as the sole element of treatment (should only be prescribed as part of an overall plan for managing obesity).

Orlistat

- Action: pancreatic lipase inhibitor, blocks the breakdown and hence the absorption of dietary fat.
- ⇒ Normally used for < 1 year
- ⇒ **Adverse effects**: faecal urgency/incontinence and flatulence.

Surgical management: bariatric surgery

Obesity - NICE bariatric referral cut-offs

- with risk factors (T2DM, BP etc): > 35 kg/m²
- no risk factors: > 40 kg/m²

Benefits

- Reduces cardiovascular mortality (the risks of long-term obesity outweigh those of surgery.)
- Indications as third line option after failure of lifestyle modifications and anti-obesity
 drugs to achieve or maintain adequate weight loss for at least 6 months + the patient
 is fit for surgery + commit to the need for long-term follow-up:
 - ⇒ BMI ≥ 40 kg/m²
 - ⇒ BMI ≥ 35 kg/m² and other significant disease (eg: type 2 DM, hypertension, sleep apnea)
- Indications as first-line option
 - ⇒ BMI > 50 kg/m2 (consider orlistat before surgery if the waiting time is long)
- Which procedures?
 - □ Laparoscopic-adjustable gastric banding (LAGB) is the <u>first-line intervention in</u>
 <u>patients with a BMI of 30-39kg/m^2</u> (produces less weight loss than malabsorptive
 or mixed procedures but as it has fewer complications)
 - ⇒ Sleeve gastrectomy (most common form of bariatric surgery) may be considered for patients with a BMI > 40 kg/m^2
 - ⇒ Primarily malabsorptive procedures (e.g. biliopancreatic diversion with duodenal switch) are usually reserved for very obese patients (e.g. BMI > 60 kg/m^2)

Lipid disorders: Overview

Causes

- Acquired (more common)
 - ⇒ Obesity
 - ⇒ Diabetes mellitus
 - ⇒ Heavy consumption of alcohol
 - ⇒ Hypothyroidism
 - ⇒ Nephrotic syndrome
 - ⇒ Cholestatic liver disease
 - ⇒ Cushing disease
 - Drugs: antipsychotics, beta blockers (e.g., metoprolol), oral contraceptive pill, highdose diuretic use
- Inherited (less common)

Pathophysiology

 Elevated LDL and reduced HDL → promote atherosclerosis → increased risk of cardiovascular events

Classification: WHO/Fredrickson classification

Classification	Aetiology	Lipid profile	Notes
Type 1 Familial Hyper- Chylomicronaemia	Deficiency of Apo CII or LPL (lipoprotein lipase)	↑ chylomicrons	typically presents with eruptive xanthoma, abdominal colic. acute pancreatitis
Type 11A Familial hypercholesterolaemia	LDL-receptor deficiency	↑TC > 7.5 ↑LDL-C > 4.9	Heterozygous type is Common Associated with tendon xanthoma
Type 11B Familial Combined Hyperlipidaemia	overproduction of apo B-100 &(VLDL) by the liver	↑ LDL ↑VLDL ↑TG	The commonest type (two thirds). Associated with glucose intolerance.
Type 111 Remnant hyperlipidaemia (dysbetalipoproteinaemia)	Abnormal ApoE	↑ IDL	palmar xanthoma is diagnostic fibrates are first line treatment
Type 1V Familial hypertriglyceridaemia	Overproduction or↓catabolism of VLDL (due to ↓ LPL)	↑TG ↑VLDL	often "polygenic". Common

abdominal pain, <u>eruptive xanthoma</u> and strong family history = think of Chylomicronaemia

Lipoproteins

- High density lipoprotein (HDL)
 - ⇒ **Secreted by** intestinal epithelium and liver
 - □ Composition: Mostly proteins and phospholipids
 - ⇒ **Function:** Transport cholesterol from peripheral tissues (e.g., atherosclerotic arteries) to the liver (reverse cholesterol transport), where it is excreted (e.g., via bile)
 - ⇒ Often referred to as "good cholesterol."
 - ⇒ Low levels of HDL are associated with an increased risk of ischaemic heart disease
 - ⇒ Among other apoproteins, HDL contains **Apo A-1**, which is found only in **HDL**.
 - - Exercise
 - modest alcohol consumption.
 - †oestrogen levels (e.g. contraceptive pill). Women have naturally higher HDL levels compared to men, due to higher oestrogen levels.
 - ⇒ Causes of ↓HDL
 - Diabetes causes low HDL
- Low-density lipoprotein (LDL)
 - ⇒ **Arise from** IDL that is modified by hepatic lipases in peripheral tissue and the liver
 - ⇒ **Composition:** Mostly cholesterol
 - ⇒ **Function:** Transport cholesterol from the liver to peripheral tissues and arteries

- ⇒ Often referred to as "bad cholesterol"
- ⇒ they carry only one apolipoprotein, Apo B-100 which binds tissue LDL receptors to facilitate receptor-mediated uptake of cholesterol.
- Intermediate-density lipoprotein (IDL)
 - ⇒ Formed from VLDL degradation
 - ⇒ Function: Transport triglycerides and cholesterol to the liver
- Very low-density lipoprotein (VLDL)
 - ⇒ Secreted by the liver
 - ⇒ Composition: Mostly triglycerides
 - ⇒ **Function:** Transport hepatic triglycerides from the liver to peripheral tissues
- Chylomicron
 - ⇒ Composition: Mostly triglycerides
 - ⇒ **Secreted by** the intestinal epithelial cells into lymphatics
 - ⇒ The nascent (early) chylomicron contains only one apoprotein, Apo B-48.
 - **⇒** Function:
 - Transport dietary triglycerides from the intestine to peripheral tissues
 - Transport dietary cholesterol to the liver in the form of triglyceride-depleted chylomicron remnants
 - ⇒ Lipoprotein lipase (LPL) hydrolyses the chylomicron into glycerol, fatty acids, and chylomicron remnant using Apo C-2 as a co-factor. **Deficiencies of LPL or Apo C-2** cause familial hyperchylomicronemia.
 - ⇒ Apo E mediates Endocytosis of chylomicron remnants

Apolipoproteins

 The following table shows the apolipoproteins present on the surface of various lipoproteins:

Lipoproteins	apolipoproteins
Chylomicron	Apo CII & Apo B48
Chylomicron remnant	Apo E
VLDL	Apo CII & Apo B100
LDL	Apo B100
IDL	Apo E & Apo B100
HDL	Apo A1

Familial Combined Hyperlipidaemia (type IIB)

Overview

- · Type IIB in Frederickson classification of inherited hyperlipoproteinemia
- Commonest type (two thirds)
- Prevalence → 1%
- Autosomal dominant
- polygenic disorder
- Pathogenesis: Defective LDL receptors or ApoB-100

Associated with: Obesity, glucose intolerance, and hyperuricaemia

Features

- Xanthelasma
- premature cardiovascular disease
- ↑ LDL, ↑VLDL, ↑TG

Treatment

• Statins (e.g. atorvastatin)

Which feature suggests a diagnosis of familial combined hyperlipidaemia (FCHL) rather than heterozygous familial hypercholesterolaemia (FH)?

→ Presence of glucose intolerance

Remnant hyperlipidaemia (type III)

Overview

- · Type III in Frederickson classification of inherited hyperlipoproteinemia
- Autosomal recessive
- Pathogenesis: Defective ApoE \rightarrow accumulation of IDL and chylomicron remnants

Features

- · Premature atherosclerosis
- Palmar and tuberoeruptive xanthomas
- ↑Total cholesterol , ↑triglycerides, ↑Chylomicrons, ↑VLDL

Diagnosis

• Definitive diagnosis can be made by **lipoprotein electrophoresis** or **genotyping of apoprotein E.**

Management

- · fibrates are first line treatment
 - \Rightarrow mode of action \rightarrow Increased lipoprotein lipase activity via PPAR-alpha (PPAR-alpha agonist)

Palmar xanthomas are pathognomonic of dysbetalipoproteinaemia (type III hyperlipoproteinemia).

Familial hypertriglyceridaemia

Overview

- Type IV in Frederickson classification of inherited hyperlipoproteinemia
- Autosomal dominant condition
- Usually due to polygenic factors
- Affects 1 in 300 people.
- Can be exacerbated by:
 - ⇒ alcohol
 - ⇒ glucocorticoids
 - ⇒ thiazide diuretics

Pathogenesis

- **Hepatic over production of VLDL**
- lipoprotein lipase (a potent metabolizer of triglycerides within VLDL) → accumulation of VLDL molecules and triglycerides.

Features

- Premature atherosclerosis
- Acute pancreatitis if triglyceride levels is very high (>11 mmol/l), likely due to pancreatic capillary obstruction.
- Features of hyperglycemia (due to abnormal glucose tolerance and insulin resistance)
- Eruptive xanthomas (yellow papules usually seen on the back, chest, and proximal extremities).
- Lipaemia retinalis (pale pink milky appearance to the retinal vessels or even to the retina itself).
- Retinal vein thrombosis

Diagnosis

- Lipid profile
 - ⇒ raised very-low-density lipoprotein (VLDL) and triglyceride levels.
 - ⇒ total cholesterol and LDL levels are typically normal

Management

- first-line →fibrates
- statins if there is mixed hyperlipidaemia

Tendon xanthomata are diagnostic hallmarks of heterozygous familial hypercholesterolaemia (FH)





Familial hypercholesterolaemia (FH)

Overview

- Type II in Frederickson classification of inherited hyperlipoproteinemia
- Autosomal dominant condition
- Caused by mutations in the gene which encodes the LDL-receptor protein.
- Heterozygous FH occur in about 1 in 300. Homozygous patients are rare
- Affect around 1 in 500 people.

Pathogenesis

Defective LDL receptors or ApoB-100, missing LDL receptors

Features

- early cardiovascular disease (CVD)
- Tuberous/tendon xanthomas (especially the Achilles tendon)
- Xanthelasma
- · High levels of LDL-cholesterol which, if untreated, may cause

Suspected diagnosis: NICE advice to suspect diagnosis of FH if:

- total cholesterol level >7.5 mmol/l
- premature coronary heart disease (<60 years) in an index individual or first-degree relative.
- children of affected parents:
 - ⇒ if one parent is affected, arrange testing in children by age 10
 - ⇒ if both parents are affected, arrange testing in children by age 5

Clinical diagnosis is now based on the Simon Broome criteria:

- Total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l plus:
 - ⇒ For definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
 - ➡ For possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels
- If LDL-C >13 mmol/l → Consider a clinical diagnosis of homozygous FH
- Two measurements of LDL-C are required to confirm the diagnosis.

The presence of tendon xanthomata and ↑LDL, ↑T.chol → familial hypercholesterolemia.

Management

- First-line: high-dose statins
 - ⇒ statins should be discontinued in women 3 months before conception due to the risk
 of congenital defects
 - ⇒ aim for at least a 50% reduction in LDL C concentration from the baseline measurement
- Second-line (if statin therapy is not tolerated or contraindicated) or if lipid not controlled by statin alone → Ezetimibe
- **Third-line:** (If statins or ezetimibe are not tolerated or contraindicated) → either a bile acid sequestrant (resin) or a fibrate
- Fourth-line: LDL apheresis: for homozygous or heterozygous FH who did not respond to drugs

- ACE inhibitors should not be used in people who are being treated with LDL apheresis. Instead, angiotensin-receptor blocking agents should be used.
- ⇒ warfarin should be discontinued 4 days before LDL apheresis and substituted with low molecular weight heparin.
- Fifth-line: Liver transplantation
- Screening for first-degree relatives (they have a 50% chance of having the disorder).
 This includes children who should be screened by the age of 10 years if there is one affected parent.
- · Lifestyle interventions: Diet
 - ⇒ total fat intake is 30% or less of total energy intake
 - ⇒ saturated fats are 10% or less of total energy intake
 - ⇒ intake of dietary cholesterol is less than 300 mg/day

Lipid-lowering therapy in patients with ACS: (2019 ESC/EAS Guidelines for the management of dyslipidaemias)

For patients who present with an ACS, and whose LDL-C levels are not at goal
despite already taking a maximally tolerated statin dose and ezetimibe, adding a
PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS
event) should be considered.

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Secondary hypertriglyceridaemia

The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.

Causes of predominantly hypertriglyceridaemia

- Obesity
 - ⇒ The commonest cause of a mild hypertriglyceridaemia is obesity secondary to a reduced efficacy of lipoprotein lipase activity and overproduction of VLDL.
 - ⇒ hypertriglyceridaemia and raised transaminases are suggestive of increased hepatic fat → associated with Non-alcoholic steatohepatitis (NASH)
- · Type 2 diabetes mellitus
 - ⇒ Bad diabetic control (↑↑ HbA_{1c)} →↓ activity of lipoprotein lipase (LPL) (<u>because LPL requires insulin for full activity</u>) → hypertriglyceridaemia and low highdensity lipoprotein (HDL)
- Alcohol
- Chronic renal failure
- Drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- Liver disease

Causes of predominantly hypercholesterolaemia

- Nephrotic syndrome
- Cholestasis
- Hypothyroidism
 - ⇒ Frank hypothyroidism is said to occur in 4% of patients with dyslipidaemias;
 - ⇒ a raised thyroid-stimulating hormone (TSH) & normal free T4 occur in 10% of patients with dyslipidaemia
 - ⇒ Total cholesterol often improves to some degree with thyroxine therapy but statins might be required as well.

High triglycerides and low high-density lipoprotein (HDL) cholesterol are the commonest lipid abnormality seen in type 2 diabetes.

Hypercholesterolaemia rather than hypertriglyceridaemia: nephrotic syndrome, cholestasis, hypothyroidism

Complications

- Increased risk of CVD events
- Increased insulin resistance

Management

- With DM → the first priority in this patient is to improve the glucose control.
- JBS2 guidelines suggest that all patients with type 2 diabetes should be prescribed a **statin**, even if their cholesterol is within the target range.
- If triglyceride level > 20 mmol/l that is not a result of excess alcohol or poor glycaemic control, refer for urgent specialist review (i.e. at a regional lipid clinic).
- If triglyceride level between 10 and 20 mmol/L:
 - ⇒ Repeat the triglyceride with a fasting test (following a meal, the chylomicron level rises in the serum which will lead to a rise in triglyceride levels)
 - ⇒ Look for secondary causes
 - ⇒ Address <u>lifestyle</u> factors: encourage weight loss, healthy diet and exercise
 - ⇒ Commence high-potency <u>statins</u> (atorvastatin, rosuvastatin) if unable to address the triglyceride level through lifestyle measures.

Fibrates (e.g. fenofibrate).

- The best initial medical treatment for hypertriglyceridemia.
- Action: PPAR <u>alpha</u> receptor agonists → increasing the activity of lipoprotein lipase
- Does not reduce cardiovascular events in the presence of diabetes, while statins have.
 Thus, an isolated hypertriglyceridaemia in the presence of significant cardiovascular risk factors, in a patient not currently on a statin, should be managed with the introduction of a statin.
- Concomitant fibrate-statin use is associated with an increased risk of myopathy.

Omega-3

- Trials of omega 3 supplementation suggest that it is associated with triglyceride reduction of up to 38%.
- OMACOR (omega-3-acid ethyl esters): Mode of action → Increases peroxisomal beta-oxidation of fatty acids in the liver
- 2019 ESC/EAS Guidelines for the management of dyslipidaemias: (In high-risk patients with TG between 1.5 and 5.6 mmol/L (135 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 2g/day) should be considered in combination with statins
- Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA).

Nicotinic acid

- it lower both cholesterol and triglyceride concentrations by inhibiting synthesis and increases HDL-cholesterol when used in doses of 1.5-3g daily.
- · It is recommended for use by specialists in combination with a statin, where a statin alone

- Add of nicotinic acid → raise HDL cholesterol level by great amount
- the value of nicotinic acid is limited by its side-effects (especially vasodilatation)
- may increase blood glucose in some patients, many mechanisms have been suggested for this:
 - ⇒ Since **nicotinic acid inhibits triglyceride synthesis**, it may be that the increased availability of free fatty acids stimulates hepatic glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source.
 - ⇒ Higher levels of fatty acids may also block glucose uptake by skeletal muscle.
 - ⇒ Direct effects on beta-cell function have also been postulated.
- For people with a triglyceride concentration between 4.5 and 9.9 mmol/L. optimize the management of other CVD risk factors present.

Which lipid abnormalities are most likely to be detected in a patient with type 2 diabetes?

- Small dense LDL molecules (LDL is not typically elevated in type 2 diabetes)
- II HDL
- ↑↑Triglycerides

Question

Analysis of a patient lipoprotein profile shows a deficiency of apolipoprotein C-II. All other lipoproteins are normal.

Which lipid profile is most likely to be shown?

Answer → Elevated levels of both chylomicrons and VLDLs

Apolipoprotein C-II (Apo C-II) is an essential co-factor of lipoprotein lipase, which hydrolyzes triglyceride in chylomicrons and VLDLs.

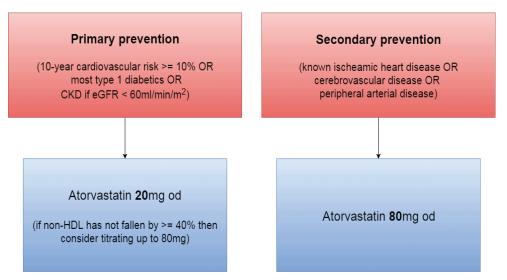
Xanthomas

- **Tuboeruptive xanthomas** occur in type III hyperlipoproteinaemia
- Eruptive xanthomas are associated with hyperchylomicronaemia (type I and type V hyperlipoproteinaemia)
- Xanthoma tendinosum, which are nodular swellings of tendons, usually occur in type II hyperlipoproteinaemia

Hyperlipidaemia: management

In the primary prevention of CVD using statin aim for a reduction in non-HDL cholesterol of > 40%

Graphic showing choice of statin.



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Statins reduce all-cause mortality (not just cardiovascular mortality) in primary prevention

Primary prevention - risk assessment

- NICE recommend use the QRISK2 CVD risk assessment tool for patients aged ≤ 84 years.
- High risk of cardiovascular disease (CVD), defined as a 10-year risk of 10% or greater.
- QRISK2 should not be used in the following situations:
 - ⇒ Patients ≥ 85 years are already at high risk of CVD due to their age
 - ⇒ type 1 diabetics
 - ⇒ patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria.
 - ⇒ patients with a history of familial hyperlipidaemia.

• NICE suggest QRISK2 may underestimate CVD risk in the following:

- ⇒ people treated for HIV
- ⇒ Serious mental health problems
- ⇒ people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs
- ⇒ Autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus.

Measuring lipid levels

- ⇒ The samples does not need to be fasting.
- ⇒ repeat sample (fasting or non-fasting) before deciding on further management

Primary prevention management (No established cardiovascular disease)

- If the QRISK2 10-year risk is ≥ 10%

 Atorvastatin 20mg should be offered first-line +
 Lifestyle changes
- People with Type 1 diabetes mellitus: atorvastatin 20 mg should be offered if type 1 diabetics who are: age > 40 years, or diabetes for more than 10 years or nephropathy or CVD risk factors.
- People with type 2 diabetes → If the QRISK2 10-year risk is ≥ 10% → atorvastatin 20 mg
- People with Chronic kidney disease (CKD): atorvastatin 20mg should be offered to all
 patients with CKD

Secondary prevention management (established cardiovascular disease)

- All patients with CVD should be taking a statin in the absence of any contraindication.
- Atorvastatin 80mg should be offered first-line.
- Follow-up patients at 3 months: if the non-HDL cholesterol has not fallen by at least 40%

 → ↑the dose of atorvastatin gradually up to 80mg.

Targets of management

	Total cholesterol	LDL cholesterol	Triglycerides
Joint British Societies	< 4.0 mmol/l	< 2.0 mmol/l	< 1.7 mmol/L

Lipid-lowering agents

Mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

Drugs	Mechanism of action	Adverse effects
Statins	HMG CoA reductase inhibitors	Myositis, deranged LFTs
Ezetimibe	Decreases cholesterol absorption in the small intestine	Headache
Nicotinic acid	Decreases hepatic VLDL secretion	Flushing, myositis
Fibrates	Agonist of PPAR-alpha therefore increases lipoprotein lipase expression	Myositis, pruritus, cholestasis
Cholestyramine	Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid	GI side-effects

PPAR-α agonists (The fibrate) $\rightarrow \downarrow$ serum triglyceride levels and ↑ HDL-cholesterol **PPAR-**γ agonists (the glitazones) $\rightarrow \downarrow$ free fatty acid levels $\rightarrow \downarrow$ insulin resistance $\rightarrow \downarrow$ blood glucose levels

Statins

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

Action

 Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

Metabolism

- Simvastatin, atorvastatin and lovastatin are mainly metabolized by cytochrome P450 (CYP) 3A4.
- Fluvastatin and rosuvastatin is metabolized by CYP2C9
- Pravastatin is excreted largely unchanged.

Pravastatin may be suitable for primary prevention, but in high-risk secondary prevention patient, a stronger agent is required such as rosuvastatin.

Adverse effects

- **Myopathy:** includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase.
 - ⇒ Occurs in up to 5%.
 - ⇒ More common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (**rosuvastatin**, **pravastatin**, fluvastatin)
 - ⇒ If only myalgia (muscle pain): continue treatment as long as creatinine phosphokinase (CK) remain normal.
 - ⇒ Before offering a statin, if CK levels are **5 times the upper limit of normal** (repeated 2 times), do not start statin treatment. If CK levels are raised but less than 5 times the upper limit of normal, **start statin treatment at a lower dose.**
 - ⇒ Starting at a low dose and gradually titrating up can also minimise the risk of side effects: for example, start at 5 mg of rosuvastatin.

Hepatotoxicity:

- ⇒ Occurs in ~ 2% of patients
- ⇒ ↑ LFTs due to the involvement of cytochrome P450 systems (CYP3A4 and CYP2C9) in the breakdown of statins
- ⇒ Check LFTs at baseline, 3 months and 12 months, but not again unless clinically indicated.
- ⇒ Statins should be discontinued if serum transaminase concentrations rise to and persist at 3 times the upper limit of the reference range. If LFT are raised but less than 3 times the upper limit of normal:
 - 1st step: NICE advises reducing the dose in the first instance.
 - 2nd step: Consider an alternative statin.
- Statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke. For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage.
 - ⇒ This effect is not seen in primary prevention.

Maintain a high index of suspicion for rhabdomyolysis if muscle pain occurs after administering statins

Drug interactions with statins

P450 inhibitors ↑ CK and myopathy

- P450 inhibitors (e.g. HIV protease inhibitors, Macrolides (especially erythromycin and clarithromycin), Azole antifungals, Cyclosporine, grapefruit juice) → ↑ serum statins → precipitate Myopathy or rhabdomyolysis
- Other lipid-lowering agents (e.g. Fibrates and Nicotinic acid)
- Agents which can precipitate Myopathy or rhabdomyolysis
 - ⇒ calcium channel blockers

Which statin is associated with the lowest risk of rhabdomyolysis?

→ Fluvastatin

Lipid lowering drugs and pregnancy

- Normally in pregnancy, cholesterol can increase by up to 50%
- Omega-3 fatty acids can be used safely in pregnancy as monotherapy, and function to decrease maternal TG levels.
- With the exception of the bile acid sequestrants (BAS) such as cholestyramine, cholesterol-lowering medications should be stopped prior to pregnancy
- NICE guidelines recommend stopping cholesterol-lowering medications 3 months before attempting to conceive.

Contraindications

- 1. Active liver disease
- 2. Muscle disorder
- Pregnancy, breastfeeding: stop taking statins 3 months before attempt to conceive and do not restart until breastfeeding is finished.

Fibrates

Agents

bezafibrate, fenofibrate, and gemfibrozil

Mechanism of action

- Activation of the peroxisome proliferator-activated receptor alpha (PPAR-α) → ↓ LDL, ↑
 HDL, ↓↓↓ triglyceride
- Enhance lipoprotein lipase activity

Indication

second-line drug of choice in hyperlipidemia, most effective for lowering triglycerides

Contraindications

- Renal insufficiency
- Liver failure
- Gall bladder diseases

Side effects

- Dyspepsia
- Myopathy
- Cholelithiasis (Cholesterol gallstones)
- ↑ LFTs (hepatotoxicity)

Interactions

 enhance the effect of other drugs by inhibiting hepatic CYP450 (e.g., sulfonylureas, warfarin)

Ezetimibe

Ezetimibe \rightarrow reduces the absorption of cholesterol through the gut.

Mechanism of action

• Blocks cholesterol reabsorption at small intestine brush border via inhibiting NPC1L1 in the gut lumen $\rightarrow \downarrow$ LDL

Indication

- Monotherapy: in contraindications or statin intolerance
- Combination therapy (statin and ezetimibe): in insufficient LDL cholesterol reduction by statins

Side effects (especially in combination therapy, otherwise rare):

- ↑ liver enzymes,
- angioedema,
- diarrhea,
- myalgia

Contraindication

coadministration with a statin during active liver disease

Nicotinic acid (niacin)

Nicotinic acid increases HDL levels

Mechanism of action

- Inhibits lipolysis and fatty acid release in adipose tissue → ↓ triglyceride and LDL synthesis,
 ↑ HDL
- Niacin lowers LDL-C and increases HDL-C by:
 - ⇒ ↓ hepatic VLDL synthesis and secretion into circulation,
 - ⇒ ⊥ lipolysis in peripheral adipose tissue.

Indication

- high LDL cholesterol and lipoprotein(a) levels (> 50 mg/dL) despite statin and ezetimibe therapy (or if statins are contraindicated)
- Nicotinic acid is highly effective at raising high density lipoprotein (HDL) cholesterol

Adverse effects

- Flushing: NSAIDs (e.g., aspirin, ibuprofen) taken 30–60 minutes before niacin can prevent flushing by inhibiting prostaglandin synthesis.
- Hyperglycemia (impaired glucose tolerance) →↑ HA1c in diabetics
- Irritates the gastric mucosa, exacerbates gastroesophageal reflux. contraindicated in patients with active peptic ulcer disease
- Mvositis
- Hyperuricemia → precipitates acute gout
- ↑ LFTs

Contraindications

- I iver failure
- Gout
- Hemorrhage
- · Gastric ulcer
- Cardiovascular instability

Cholestyramine

Mechanism of action

- · bile acid sequestrant
- bind bile acids in the intestine to prevent reabsorption and recycling
 - ⇒ forces liver to consume cholesterol in the process of making more bile salts
 - ⇒ binds bile acids in the intestine → interruption of enterohepatic circulation (↓ bile acid absorption and ↑ bile acid excretion) → lowers cholesterol
- The main effect on lipid profile → reduce LDL cholesterol (↓ unbound LDL),
 - ⇒ causes ↑ in LDL-receptor synthesis

Indications

- management of hyperlipidaemia.
 - ⇒ Combination treatment with statins in hypercholesterinemia
- · Digitoxin overdose
- Pruritus associated with elevated bile acid levels (cholestasis)
- · Bile acid diarrhea
- Bowel obstruction
- occasionally used in Crohn's disease for treatment resistant diarrhoea.

Adverse effects

- · abdominal cramps and constipation
- decreases absorption of fat-soluble vitamins (e.g: vitamin D absorption will be reduced)
 - ⇒ consider fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation
- · cholesterol gallstones
- ↑ LFTs
- Myalgia
- · may raise level of triglycerides

Contraindications

- Hypertriglyceridemia > 300–500 mg/dL
- Hypertriglyceridemia-induced pancreatitis

Tangier disease

Overview

- · rare autosomal recessive metabolic disorder.
- also known as familial alpha-lipoprotein deficiency or hypoalphalipoproteinemia

Features

- Decreased levels or even a complete absence of high-density lipoproteins (HDL)
- · Low cholesterol levels
- cholesterol ester depositions especially in:
 - ⇒ Tonsils → enlarged, yellow-orange tonsils.
 - ⇒ Liver and spleen resulting in hepatosplenomegaly.

Abetalipoproteinemia

Treatment of abetalipoproteinemia involves dietary restriction of fats, and high-dose vitamin E therapy

Pathophysiology

- Rare autosomal recessive disorder
- Mutation in the microsomal <u>triglyceride transfer protein</u> → <u>deficiency of apolipoprotein B-48 and B-100</u> (both necessary for chylomicron formation and fat absorption) → deficiency of LDL, VLDL and chylomicrons.

Features

Typically presents in <u>early childhood</u> with steatorrhea, abdominal distension, and failure to thrive. During <u>childhood or adolescence</u>, progressive ataxia, neuropathy, and vision impairment develop.

- Neurologic: caused by deficiency of vitamin E)
 - ⇒ cognitive decline
 - ⇒ Clumsiness may be the first neurologic manifestation
- Low visual acuity, caused by:
 - ⇒ Retinitis pigmentosa → do fundoscopy
 - ⇒ Vitamin A deficiency

Treatment

- high-dose vitamin E
- other fat-soluble vitamins (A, K, and D) should also be supplemented
- restriction of long-chain fatty acids

Disease associations with low LDL-C include malignancy and malabsorption

Causes of hypocholesteraemia

- Acquired:

 - ➡ Malabsorption (Short-bowel syndrome, blind loop syndrome, celiac disease, pancreatic exocrine insufficiency, giardiasis)
 - ⇒ Anaemia (Thalassemia, pernicious anaemia)
 - ⇒ Chronic infection and infestations
 - ⇒ Severe illness in hospitalised patients
- Genetic:
 - ⇒ Hypobetalipoproteinemia (most common genetic cause),
 - ⇒ Abetalipoproteinemia

Gynaecomastia

Definition

 Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen: androgen ratio.

Causes

 It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia

- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's (47, XXY karyotype)
- · testicular failure: e.g. mumps
- liver disease

- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- starvation/refeeding
- · drugs: see below

Drug causes of gynaecomastia (10-25% of cases)

Relatively Common causes

- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- diamorphine
- cyproterone
- finasteride
- gonadorelin analogues e.g. Goserelin, buserelin
- · oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia

- tricvclics
- isoniazid
- · calcium channel blockers
- heroin
- busulfan
- methyldopa

September 2010 exam: H/O developed excessive amounts of breast tissue bilaterally. Which one of the following drugs is most likely to be responsible? Goserelin (Zoladex)

Physiological changes during pregnancy – endocrine

pregnancy → ↑ oestradiol & prolactin + ↓ LH/FSH.

Progesterone

- Responsible for pregnancy maintenance
- Produced by the corpus luteum until the 10–12 weeks of gestation, after which it is produced by the fetoplacental unit

Human placental lactogen: a hormone synthesized by syncytiotrophoblasts of the placenta, which promotes the production of insulin-like growth factors.

- · Increases insulin levels
- · Causes insulin resistance

- Increases serum glucose levels and lipolysis to ensure sufficient glucose supply for the fetus
- Maternal insulin resistance begins in the second trimester and peaks in the third trimester.

Pituitary gland

 Hyperplasia of lactotroph cells in the anterior pituitary → physiological enlargement of the pituitary gland (up to 40% increase from pregestational volume)

Thyroid gland

- Thyroid gland hypertrophy
 - ➡ The thyroid gland needs to produce 50% more thyroid hormone during pregnancy to maintain an euthyroid state.
 - ⇒ A 10–20% increase in thyroid mass occurs.
- . Increase in thyroid-binding globulin and albumin due to increased hepatic synthesis.
 - ⇒ Pregnancy → ↑↑ thyroxine-binding globulin (TBG) → ↑↑ total thyroxine but does not affect the free thyroxine level
- Increase in total T3 and T4
 - ⇒ in normal pregnancy (T₃) and T₄ levels show a slight increase with suppressed (TSH) in the first trimester due to the partial thyroid-stimulating action of human chorionic gonadotrophin (beta-HCG).
 - ⇒ Free T3 and T4 remains within normal ranges
- β-hCG-mediated hyperthyroidism (↓TSH)
 - ⇒ β-hCG molecule has a similar structure to that of the TSH molecule. β-hCG binds to TSH receptors of the thyroid gland → thyroid stimulation → hyperthyroidism
- Factors influence thyroid function tests in the pregnant patient.
 - ⇒ thyroid stimulatory effects of hCG.
 - HCG → activation of the TSH receptor → <u>transient gestational</u> hyperthyroidism.
 - HCG levels will fall in second and third trimester

Lipids

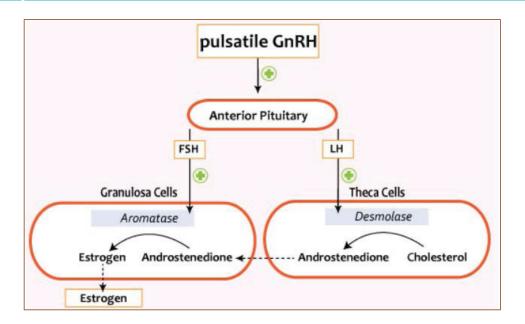
• ↑ Triglycerides and cholesterol (due to increased lipolysis and fat utilization)

↑ SHBG (Sex hormone-binding globulin) and corticosteroid-binding globulin

Beta-HCG has a degree of thyroid stimulating activity →↓↓ TSH. No intervention is needed

Physiological effects of LH, FSH, and sex hormones

- ♀: Ovaries
 - **❖ FSH:** follicular maturation → ↑ **estrogen**
 - ❖ LH: ↑ estrogen, ovulation, and ↑ progesterone
- d: Testicles
 - **❖ FSH:** production of sperm, ↑ **inhibin**
 - **❖ LH:** stimulation of Leydig cells → ↑ **production of testosterone**



Dihydrotestosterone (DHT)

Composition

Testosterone is a steroid hormone and can be converted to oestradiol.

Production

LH stimulates testosterone production and FSH spermatogenesis

Binding

 It binds to intracellular receptors and is mostly bound to <u>sex-hormone binding globulin</u> (SHBG)

Conversion

- Testosterone converted to dihydrotestosterone (DHT) in the body by the enzyme 5α-reductase. DHT is a more active compound than testosterone.
- The absence of 5α-reductase or the absence of DHT receptors leads to testicular feminisation.

Function

- During fetal development and early life: differentiation of the penis, scrotum, and prostate.
- expression of male secondary sex characteristics
- During late adulthood: <u>prostate growth</u>, <u>male pattern baldness</u>, and <u>sebaceous gland</u> <u>activity</u>.

Deficiency

- → testosterone is due to either:
 - ⇒ ↓ free level due to ↓ production (Leydig and pituitary dysfunction) (Lead to ↑ synthesis of SHBG)
 - increasing age: total testosterone concentrations fall slightly, and free testosterone fall more.
 - \Rightarrow ↓ activity at receptor often due to androgen receptor deficiency (<u>5α-reductase</u> deficiency).

- Patients with 5α-reductase deficiency will have ambiguous genitalia at birth until they reach puberty, when the testosterone surge causes growth of external male genitalia, however, these patients are otherwise healthy. Individuals with this deficiency sometimes change their gender role in adolescence.
 - obesity (hyperinsulinaemia of obesity → ↓SHBG levels → ↓testosterone (low SHBG and normal free testosterone)

Evaluation

- Initial evaluation: serum testosterone in the early morning, fasting.
- Testosterone levels vary according to the <u>degree of binding to albumin and SHBG</u>; (↑SHBG
 →↑total testosterone when testosterone production is low-).
- The equilibrium dialysis method is most useful for measurement of free testosterone (not bound to protein)
- If the testosterone is low:
 - ⇒ measurement of **LH** and **FSH** to determine if the hypogonadism is primary or secondary. If secondary → assessment of other pituitary hormones.
 - ⇒ If the patient has multiple pituitary hormonal deficiencies and/or if the testosterone is less than 200 ng/dL, we suggest *MRI* of the sella.

Testosterone therapy

- Indications
 - ⇒ hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
 - ⇒ Older men (>65 years) with age-related decline in testosterone concentration:
 - routinely prescribing testosterone therapy is not recommended
 - In symptomatic (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone, testosterone therapy may be offered on an individualized basis after discussion of the potential risks and benefits.
 - HIV-infected men with weight loss and low testosterone (when other causes
 of weight loss have been excluded) to induce and maintain body weight and
 lean mass gain.

Target

- ⇒ For patients receiving testosterone enanthate, the <u>testosterone level</u> should be <u>between 400 and 700 ng/dL at about half-way between administrations</u> (one week after injection) which are generally given every two weeks.
- Which type of testosterone therapy is most likely to result in an increase in dihydrotestosterone level?
 - \Rightarrow Dihydrotestosteone levels increase with the use of a testosterone **scrotal patch** due to the high concentration of $\underline{5\alpha}$ -reductase in genital skin. Levels may return to normal after discontinuation; however, they often remain elevated.

· Benefits of testosterone treatment

- ⇒ ↑sexual interest and activity, slight improvement in walking, slight improvement in mood, ↑ hemoglobin, and ↑ bone mineral density (BMD).
- ⇒ No change in energy or cognition is expected.

Side effects

- ⇒ Erythrocytosis leading to <u>elevated haematocrit</u>
 - Haematocrit should be measured 3-6 months after initiating therapy and yearly thereafter.
 - Guidelines suggest that if haematocrit is increased and no other underlying cause is found, the dose should be down-titrated.
- ⇒ PSA
 - Androgen replacement therapy is contraindicated in patients with prostate cancer and breast cancer.

- Urological consultation is recommended if:
 - PSA > 1.4 ng/mL within a 12-month period,
 - a PSA velocity > 0.4 ng/mL/year using the level after 6 months of testosterone therapy as the reference
 - abnormality on digital rectal examination, or
 - an I-PSS score of greater than 19.

Polycystic ovarian syndrome (PCOS)

Polycystic ovarian syndrome - ovarian cysts are the most consistent feature

Infertility in PCOS - clomifene is superior to metformin

Incidence

• affect between 5-20% of women of reproductive age.

Aetiology

- · not fully understood
- Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS

Features

- Oligo/amenorrhoea 70%
- hirsutism, acne (due to hyperandrogenism) 60%
- obesity 35%
- subfertility and infertility 30%.
 - Chronic anovulation is the mechanism for infertility
- acanthosis nigricans (due to insulin resistance)
- psychological symptoms
- Clitoromegaly is seen occasionally in PCOS but is normally associated with very high androgen levels. If clitoromegaly is found, then further investigations to exclude an ovarian or adrenal androgen secreting tumour are required.

Investigations

- pelvic ultrasound: multiple cysts on the ovaries
 - ⇒ transvaginal ultrasound is said to have 91% diagnostic sensitivity
 - ⇒ The presence of more than eight follicular cysts of less than 10 mm and increased ovarian stroma is sufficient to make the diagnosis.
- FSH, LH, prolactin, TSH, and testosterone are useful investigations:
 - ⇒ FSH will be normal or low, while LH will be elevated.
 - Increased LH causes hyperplasia of ovarian theca cells.
 - Increased LH causes increased testosterone and androstenedione
 - Raised LH: FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis.
 - LH/FSH ratio is normally about 1:1 in premenopausal women, but with PCOS a ratio of greater than 2:1 or 3:1 may be considered diagnostic.
 - ⇒ Prolactin may be normal or mildly elevated.
 - 10% of patients with PCOS have hyperprolactinaemia,
 - elevation in prolactin due to the low oestrogen <u>stimulating GnRH</u>, which in turn stimulates the anterior pituitary hormones including prolactin.

- However, the elevation in prolactin in PCOS rarely exceeds 1000 mU/l.
- ⇒ Testosterone may be normal or mildly elevated however, if markedly raised consider other causes
 - The appropriate initial biochemical investigation
 - Normal or elevated testosterone, but with a low sexhormone-binding globulin (SHBG) level, resulting in a high free androgen index.
- ⇒ Sex hormone-binding globulin (SHBG) is frequently low
 - (SHBG) is a transporter protein that binds to both testosterone and oestradiol;
 - it is reduced in insulin resistance, which is common in (PCOS).
 - (SHBG) is low in 50%, due primarily to hyperinsulinaemia.
 - The reasons include that androgens reduce the globulin production, whereas oestrogen promotes production.
 - Many women with PCOS have a high-normal or even a normal total testosterone, but a low SHBG because they have insulin resistance.
- ⇒ hyperestrogenism
 - Increased androstenedione/testosterone in PCOS can be peripherally converted in adipose tissue to estrone by aromatase.
 - increased circulating levels of estrone → endometrial hyperplasia which is a precursor to endometrial carcinoma

Impaired glucose tolerance

- ⇒ hyperinsulinaemia (insulin resistance → high circulating insulin levels due to peripheral insulin resistance).
- ⇒ Up to 40% of women with PCOS have impaired glucose tolerance,
- ⇒ up to 10% develop frank Type 2 diabetes mellitus

long term complication of PCOS:

- risks of diabetes (due to peripheral insulin resistance),
- sleep apnoea,
- endometrial cancer,
- mental health disorders.

Diagnostic criteria

- According to the Rotterdam Consensus, two of the following three criteria are required for the diagnosis of the PCOS:
 - 1. oligo-/anovulation
 - 2. hyperandrogenism
 - clinical (hirsutism or less commonly male pattern alopecia) or
 - biochemical (raised free androgen index or free testosterone)
 - 3. polycystic ovaries on ultrasound.

Management

- General
 - ⇒ Weight reduction: **the gold-standard treatment for PCOS**. A loss in weight of only 5% reduces hirsutism by up to 40%.
- For associated hirsutism
 - Dianette® (cyproterone acetate) combined oral contraceptive pill (COC) is the most effective
 - o if doesn't respond to COC then topical effornithine may be tried
 - Spironolactone, flutamide and finasteride may be used for its antiandrogenic properties

- · For infertility

 - ⇒ First- line drug: Anti-oestrogen therapies such as clomifene → the most effective treatment
 - work by occupying hypothalamic oestrogen receptors without activating them.
 This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion
 - ⇒ Second-line drug: Metformin is also used, either combined with clomifene or alone, particularly in patients who are obese but is not a first line treatment
 - ⇒ Gonadotrophins: usually reserved for patients who are resistant to clomifene

MRCPUK-part-1-May 2009 exam: H/O infertility with PCOS. Apart from advising her to lose weight, which intervention is most effective in increasing her chances of conceiving? Clomifene (if clomifene – the first line - is not an option, metformin – the second line - is the right answer)

September 2009 exam: Which finding is most consistently seen in polycystic ovarian syndrome? Ovarian cysts on ultrasound

MRCPUK-part-1-January 2012 exam: What is the mechanism of action of metformin in PCOS? Increases peripheral insulin sensitivity

Hirsutism

Hirsutism is often used to describe androgen-dependent hair growth in women Hypertrichosis used for androgen-independent hair growth

Definition

 Excessive male pattern hair growth in women (e.g., on the chin, above the upper lip, and around the umbilicus)

Causes

- Idiopathic (the most common): normal menstrual cycle, normal serum androgen, , and no identifiable cause hirsutism.
- Polycystic ovarian syndrome is the most common identifiable causes of hirsutism
- Excess androgen (10% of cases): hirsutism, acne, menstrual dysfunction, alopecia.
 - ⇒ Cushing's syndrome
 - ⇒ congenital adrenal hyperplasia
 - ⇒ androgen therapy
 - ⇒ obesity: due to peripheral conversion oestrogens to androgens
 - ⇒ androgen secreting ovarian tumour
- Drugs

Assessment of hirsutism

- Mild hirsutism and normal menses → do not require laboratory workup and can be treated empirically.
- Moderate or severe symptoms → early morning total testosterone level
 - ⇒ if moderately elevated, it should be followed by a plasma free testosterone level.
 - ⇒ A total testosterone level greater than 200 ng per dL (6.94 nmol per L) should prompt evaluation for an androgen-secreting tumor.

• Testing for endocrinopathies and neoplasms, such as polycystic ovary syndrome, adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, and androgen-secreting tumors.

Management

- Advise weight loss if overweight
- Hair removal (Shaving)
- Pharmacologic measures
 - ⇒ Combined oral contraceptive pills: first-line pharmacologic treatment
 - ⇒ Facial hirsutism: topical eflornithine contraindicated in pregnancy and breast-feeding
 - ⇒ Treatment response should be monitored for at least six months before making adjustment.

Hypertrichosis

Definition

 excessive <u>hair growth above the normal</u> for the age, sex and race of an individual, in contrast to <u>hirsutism</u>, which is excess hair growth <u>in women</u> following a male distribution pattern.

Causes

- Drugs:
 - ⇒ phenytoin
 - ⇒ minoxidil (antihypertensive vasodilator. also used to treat androgenic alopecia →
 slows hair loss and promotes hair regrowth)
 - ⇒ ciclosporin
- Congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
- Metabolic disorders
 - ⇒ thyroid dysfunction
 - ⇒ porphyria cutanea tarda
 - ⇒ anorexia nervosa

Treatment

Hair removal

Amenorrhoea

Primary amenorrhoea

- Definition: failure to start menses by the age of 16 years
- Causes
 - ⇒ Turner's syndrome
 - ⇒ testicular feminisation
 - ⇒ congenital adrenal hyperplasia
 - ⇒ congenital malformations of the genital tract

Secondary amenorrhoea

- Definition
 - ⇒ absence of menses for more than 3 months (in women with previously <u>regular</u> cycles) or 6 months (in women with previously <u>irregular cycles</u>)
- Causes
 - ⇒ Pregnancy → most common cause of secondary amenorrhea
 - ⇒ hypothalamic amenorrhoea (e.g. Stress, excessive exercise) → ⊥ FSH

Weight-related amenorrhoea

- ⇒ amenorrhoea can even be seen at the lower end of the normal range.
- ⇒ often seen in ballet dancers, who maintain a low weight and undergo periods of extreme physical exercise.
- ⇒ Gaining body weight to above the 50th centile for height normally results in the restoration of menstruation, but if this cannot be achieved oestrogen replacement might be considered.
- ⇒ polycystic ovarian syndrome (PCOS)
- ⇒ hyperprolactinaemia
- ⇒ premature ovarian failure → ↑ FSH
- ⇒ thyrotoxicosis (hypothyroidism may also cause amenorrhoea)
 - Hypothyroidism (\downarrow T3/T4 \rightarrow ↑ TRH \rightarrow ↑ prolactin \rightarrow \downarrow GnRH \rightarrow \downarrow estrogens)
- ⇒ Sheehan's syndrome
- ⇒ Asherman's syndrome (intrauterine adhesions)

Initial investigations

- · exclude pregnancy with urinary or serum bHCG
- gonadotrophins: low levels indicate a hypothalamic cause whereas raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
- prolactin
- androgen levels: raised levels may be seen in PCOS
- oestradiol
- · thyroid function tests

Primary ovarian failure means that the patient never has a normal menstrual cycle, and has the triad of

- 1. amenorrhea.
- 2. hypergonadotropinism,
- 3. hypoestrogenism.

Premature ovarian failure

The history of prolonged cessation of menses with a normal weight, normal thyroid function tests and a history of coeliac disease is pointed to a diagnosis of premature ovarian failure

Criteria for diagnosis

- 1. age under 40 years
- 2. menopausal symptoms (including no or infrequent periods)
- 3. and elevated FSH levels on 2 blood samples taken 4–6 weeks apart.

Epidemiology

occurs in around 1 in 100 women.

Causes

- idiopathic the most common cause
- chemotherapy
- autoimmune
- radiation

Features

- · secondary prolonged amenorrhoea
- infertility
- climacteric symptoms: hot flushes, night sweats

Investigations

- raised FSH, LH levels
- ↓↓oestradiol
- sex hormone releasing hormones would be elevated in an attempt to drive LH and FSH release.

Treatment

- Hormone replacement therapy (HRT) or a combined hormonal contraceptive to protect against osteoporotic fracture.
 - ⇒ HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
 - ⇒ both HRT and combined oral contraceptives offer bone protection
 - ⇒ HRT is not a contraceptive.
- Spontaneous recovery of fertility is unlikely (occurs in only 5%).

Menopause

Definitions

- Peri-menopause → aged over 45, vasomotor symptoms and irregular periods
- menopause → aged over 45, no period for at least 12 months, not associated with a
 pathology and not using hormonal contraception.

Symptoms

- Usually preceded by 4–5 years of abnormal menstrual cycles.
- vasomotor symptoms (e.g. hot flushes and sweats): most common
- musculoskeletal symptoms (for example, joint and muscle pain)
- effects on mood (e.g. low mood)
- urogenital symptoms (e.g. vaginal dryness)
- Sexual difficulties (e.g. low sexual desire).
- Women with obesity tend to suffer from <u>fewer</u> symptoms in menopause due to peripheral conversion of androgens to estrogen in adipose tissue.
- Most symptoms will disappear spontaneously within 5 years after onset.

Consequences

- ↓↓ bone mineral density → osteoporotic fractures.
- ischaemic heart disease,
- ↓↓ insulin sensitivity
- ↑↑ thrombotic tendency.
- Increased possibility of developing Alzheimer's dementia
 - ⇒ Oestrogen deficiency might play a role in the development of dementia.

Investigations

- ↓ estradiol, ↓ progesterone, ↓ inhibin B
- ↑ GnRH, ↑↑ FSH and ↑LH (↑↑FSH is specific for menopause)
- Vaginal pH > 4.5
- Lipid profile: ↑ total cholesterol, ↓ high-density lipoprotein (HDL)
- Testosterone and prolactin levels are within normal ranges (androstenedione is produced by ovarian stromal cells and the adrenal glands.)

Management

- Vasomotor symptoms →hormone replacement therapy (HRT)
 - ⇒ women with a uterus → oestrogen and progestogen
 - ⇒ Women without a uterus →Oestrogen alone.
- Psychological symptoms → low mood or anxiety → HRT & CBT
 - ⇒ women with low sexual desire → testosterone supplementation if HRT alone is not effective.
- Urogenital atrophy → vaginal oestrogen (including those on systemic HRT), also in whom systemic HRT is contraindicated.

The ovaries' failure to produce estrogen begins in the late 30s and progresses to the degree that most women have near-complete loss of estrogen production by their mid-50s.

Whereas taking estrogen alone increases the risk of endometrial cancer, taking both estrogen and a progestogen in combination, as in most birth control pills, decreases the risk.

All postmenopausal women above the age of 65 should be screened for osteoporosis (i.e., using the DEXA scan to measure bone mineral density).

Hormone replacement therapy (HRT)

Main indication for HRT: control of vasomotor symptoms

HRT: unopposed oestrogen increases risk of endometrial cancer

HRT: adding a progestogen increases the risk of breast cancer

 Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen, combined with a progestogen (in women with a uterus), to help alleviate menopausal symptoms.

Unopposed oestrogen therapy is most appropriate for patient who had a hysterectomy and combined hormone replacement therapy (HRT) is unnecessary.

Indications

- vasomotor symptoms such as flushing, insomnia and headaches (The main indication)
- Premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis

Types

- Estrogen therapy: for women who have had a hysterectomy
- Estrogen plus progestin therapy: for women with a uterus

Advantages of hormone replacement therapy (HRT)

- 1. improvement in menopausal symptoms
- 2. protection against fractures of the wrist, spine, and hip secondary to osteoporosis.
- 3. reduce incidence of colorectal cancer
- 4. reduce incidence of Alzheimer's
- Hormone replacement therapy and effects on bone mass
 - ⇒ Reduction in total-body bone mass begins in women in their late twenties
 - ⇒ This loss is accelerated at the menopause
 - ⇒ Both trabecular bone loss at the level of the vertebrae and cortical bone loss at the radius are prevented by oestrogen therapy
 - ⇒ The risk of osteoporotic fractures is reduced, but not eliminated, by oestrogen therapy
 - ⇒ If the uterus has been removed in a patient, there is no need for additional progesterone therapy
 - The effect of oestrogens on bone loss may be reduced after 10 years of oestrogen therapy

Adverse effects

- Cancer
 - ⇒ Unopposed estrogen can result in endometrial hyperplasia → increased risk of endometrial cancer
 - ⇒ Estrogen plus progestin therapy → increased risk of breast cancer
- Thromboembolism: Cardiovascular disease: coronary heart disease, deep vein thrombosis, pulmonary embolism, stroke

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

- Mechanism of action
 - ⇒ estrogen antagonist in breast and endometrium
 - ⇒ **agonist** in bone to increase mineralisation
- Clinical use
 - ⇒ osteoporosis in menopausal women
 - ⇒ breast cancer prevention in women high risk for breast cancer

Toxicity

- ⇒ ↑ risk of venous thromboembolism
- ⇒ induces menopause →hot flashes

Tamoxifen

- Mechanism of action
 - mixed oestrogen-receptor antagonist and partial agonist depending on the target tissue
 - estrogen antagonist in breast
 - estrogen agonist in endometrium and bone
- Clinical use
 - ⇒ estrogen and progesterone receptor positive breast cancer
 - ⇒ breast cancer prevention in women high risk for breast cancer
- Toxicity
 - ⇒ ↑ risk of venous thromboembolism
 - ⇒ ↑ risk of endometrial cancer secondary to agonist activity
 - ⇒ induces menopause →hot flashes

Androgen insensitivity syndrome

The testosterone which is in the male range, the history of hernias as a baby and absence of acne or secondary sexual hair are all pointers towards androgen insensitivity syndrome.

The presence of **breast development** in the **absence of secondary sexual hair**, with a history of **hernias** as a child is suggestive of a diagnosis of **androgen insensitivity syndrome**. It is likely that the hernias were related to **undescended testes**. The vagina is blind ended, and there are no ovaries.

Pathophysiology

- X-linked recessive mutation of the gene encoding the androgen receptor (AR gene) →
 Defects in the androgen receptor → end organ insensitivity to androgens. end-organ
 resistance to testosterone causing genotypically male children (46XY) to have a female
 phenotype.
- Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- · Primary amenorrhoea
- Undescended testes causing groin swellings, Cryptorchidism (absence of one or both testes from the scrotum)
- External genitalia ranges from normal female to female with clitoromegaly, to underdeveloped male (hypospadias) → Associated with abdominal hernias.
- Breast development may occur as a result of conversion of testosterone to oestradiol
- Blind-ended vaginal pouch, uterine and fallopian tube agenesis (due to testicular anti-Mullerian hormone secretion)
- · Scant or no pubic hair

Diagnosis

- · High level of LH
- ↑ Oestrogen
- Normal/↑ testosterone levels (no virilization)
- Buccal smear or chromosomal analysis to reveal 46XY genotype

Management

- · Counselling raise child as female
- Bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- Oestrogen therapy

Disorders of sex hormones

The table below summarises the findings in patients who have disorders of sex hormones:

Disorder	LH	Testosterone
Primary hypogonadism (Klinefelter's syndrome)	High	Low
Hypogonadotrophic hypogonadism (Kallman's syndrome)	Low	Low
Androgen insensitivity syndrome	High	Normal/high
Testosterone-secreting tumour	Low	High

Menstrual cycle

The menstrual cycle may be divided into the following phases:

	Follicular phase (proliferative phase) (from day 1 until day 14)	Luteal phase (secretory phase) (From day 15 until day 28)
Ovarian histology	 A number of follicles develop. One follicle will become dominant around the mid-follicular phase 	Corpus luteum
Endometrial histology	Proliferation of endometrium	Endometrium changes to secretory lining under influence of progesterone
Hormones	 A rise in FSH results in the development of follicles which in turn secrete oestradiol When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation Graafian follicle is a large mature tertiary follicle containing an oocyte that is ready to be ovulated. Ovulation occurs 14 days before menses, regardless of cycle length. estradiol stimulates the growth of the endometrium. Progesterone levels are low FSH activates aromatase within 	 corpus luteum produces (3 hormones) estrogen, inhibin, and progesterone. progesterone is significantly higher than in other phases of the menstrual cycle. If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall

	Follicular phase (proliferative phase) (from day 1 until day 14)	Luteal phase (secretory phase) (From day 15 until day 28)
	 granulosa cells, increasing estradiol production. The main hormone controlling the follicular phase is estradiol, secreted by Granulosa cells. 	
Cervical mucus	 Following menstruation the mucus is thick and forms a plug across the external os Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit 	Under the influence of progesterone it becomes thick, scant, and tacky
Basal body temperature	Falls prior to ovulation due to the influence of oestradiol	Rises following ovulation in response to higher progesterone levels

Which hormone levels would be most likely to indicate the occurrence of ovulation?

→ Luteinising hormone

At which point in the menstrual cycle do progesterone levels peak?

- → Luteal phase
 - ⇒ Progesterone is secreted by the corpus luteum following ovulation.

Which mechanism is most likely responsible for the missed period in early pregnancy?

→ Syncytiotrophoblast produces human chorionic gonadotropin (hCG), which stimulates progesterone production by the corpus luteum.

Hypogonadism

Primary hypogonadism (Hypergonadotropic hypogonadism)

if LH and FSH are not elevated a primary hypogonadism is excluded.

- **Pathophysiology**
 - ⇒ gonadal insufficiency (↓ testosterone, ↓ estrogen) → ↑ gonadotropin secretion (↑) FSH and ↑ LH) from the anterior pituitary (lack of negative feedback from the impaired gonads)
- Causes
 - ⇒ Congenital abnormalities: (Primary gonadal insufficiency):
 - Turner syndrome (females)
 - Klinefelter syndrome (males)
 - androgen insensitivity syndrome
 - ⇒ Acquired diseases: (Secondary gonadal insufficiency) →(damage to leydig cells or ovarian tissue):

- Medications (Radiation, chemotherapy, Ketoconazole, Glucocorticoids, toxins)
- Autoimmune disease
- Infections (mumps, tuberculosis)
- Tumour, infiltration (Testicular tumour)
- Chronic systemic illnesses (eq: Hepatic cirrhosis, Chronic renal failure)
- Ageing: Andropause (↓ testosterone with age >50).
- Primary testicular failure (idiopathic failure).
- Investigations
 - ↑LH & FSH + ↓ testosterone + ↓ sperm count
 - ⇒ Testicular ultrasound (the most important investigation after blood hormones)

Secondary hypogonadism (hypogonadotrophic hypogonadism)

In male patients with low libido have been found to have a low testosterone first line investigation should include prolactin and LH to assess for a central cause

- Pathophysiology
 - \Rightarrow \downarrow pituitary gonadotropins (\downarrow FSH and \downarrow LH) \rightarrow \downarrow testosterone and \downarrow estrogen
- Causes
 - ⇒ Genetic defects: (e.g., Kallmann syndrome, Prader-Willi syndrome, Gaucher disease)
 - ⇒ Hypothalamic and/or pituitary lesions due to: Neoplasm (e.g. prolactinoma, craniopharyngioma, astrocytoma)
 - ⇒ Malnutrition (e.g., anorexia nervosa)
 - ⇒ Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis, diabetes and obesity.)
- Investigations
 - ⇒ serum testosterone and sperm count are subnormal + normal or reduced LH and FSH
 - ⇒ Prolactin level (↑Prolactin reduces LH and FSH)
 - ⇒ measure of **free testosterone** (as total testosterone can be low due to SHBG being decreased in obesity and with ageing).
 - ⇒ Pituitary MRI: the best image to exclude other pituitary pathology.

Clinical features

- Delayed puberty
- Developmental abnormalities with genitalia (undescended testes, hypospadias)
- Infertility (⊥ sperm count), impotence, and/or ⊥ libido
- · Secondary amenorrhea

Treatment

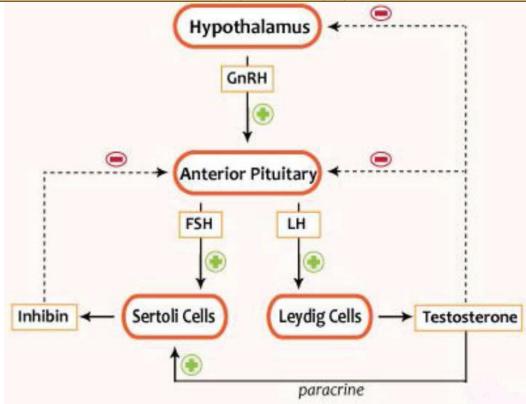
- Treat underlying cause: e.g., surgical excision of tumors, pharmacotherapy for prolactinomas
- Hormone replacement therapy

Poor ability to concentrate is most consistent with post-pubertal loss of testicular function, whereas (High-pitched voice, Gynecomastia, Disproportionately long arms and legs, Scant pubic and axillary hair) are most consistent with hypogonadism that develops before puberty.

Tip to remember

Testosterone and LH levels can help distinguish between different causes of abnormal sexual development:

- 1- High testosterone and high LH: defective androgen receptor (androgen insensitivity syndrome)
- 2- High testosterone and low LH: testosterone-secreting tumor
- 3- Low testosterone and high LH: primary hypogonadism
- 4- Low testosterone and low LH: hypogonadotrophic hypogonadism



Delayed puberty

The first visible sign of puberty in males is testicular enlargement, while in females it is breast development.

Definition

 Absent or incomplete development of secondary sex characteristics by the age of 14 years in boys or 13 years in girls

Causes

- Constitutional delay of growth and puberty (normal variants of growth): the most common cause of delayed puberty
- Primary/ hypergonadotrophic hypogonadism: e.g. Klinefelter's and Turner's syndromes.
- Secondary/ hypogonadotrophic hypogonadism: causes
 - ⇒ Genetic defects: (e.g., Kallmann syndrome, Prader-Willi syndrome, Gaucher disease)
 - ⇒ Malnutrition (e.g., anorexia nervosa)
 - ⇒ Chronic diseases (e.g., inflammatory bowel disease, hypothyroidism, cystic fibrosis)

Delayed puberty with short stature	Delayed puberty with normal stature
Turner's syndrome	polycystic ovarian syndrome
Prader-Willi syndrome	androgen insensitivity
Noonan's syndrome	Kallman's syndrome
	Klinefelter's syndrome

Features

- Signs of delayed puberty in girls include:
 - ⇒ Absence of breast development by age 14 years
 - ⇒ Pubic hair absent by age 14
 - ⇒ More than five years between the start and completion of breast growth
 - ⇒ Menarche has not occurred by age 16.
- Signs of delayed puberty in boys include:
 - ⇒ No testicular enlargement by age 14 years
 - ⇒ Pubic hair absent by age 15
 - ⇒ More than five years between the start and completion of growth of the genitalia.

Diagnosis

- Primary hypogonadism → ↓gonadal hormones (testosterone in boys and estradiol in girls)
 + ↑ luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- Secondary hypogonadism → ↓hypothalamic gonadotropin-releasing hormone (GnRH) → low to normal LH and FSH → ↓gonadal hormones
- Constitutional delay is usually assessed using a bone age assessment (radiography of the hand and wrist) and measuring the patterns of ossification at the epiphyses of the bones of the hands → delayed bone age.

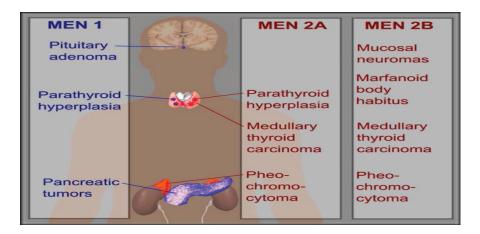
Management

- · Constitutional delay: Observation
- Organic delay: Sex-steroid therapy to induce puberty + lifelong hormone replacement therapy after puberty

Multiple endocrine neoplasia

Genetic inheritance

- Autosomal dominant disorder, high penetrance
- The table below summarises the three main types of multiple endocrine neoplasia (MEN)



Type 1 multiple endocrine neoplasia (MEN 1)

- a defect in the gene MEN1, a tumor-suppressor gene found on chromosome 11 that codes for menin protein.
- For MEN1, remember the triad of three Ps, which includes pituitary, parathyroid, and pancreatic tumors.
 - ⇒ Pituitary tumors → ↑prolactin → galactorrhea, decreased libido, or infertility.
 - ⇒ Hyperparathyroidism is the most common manifestation in MEN 1 (occurs in 90% of cases) → hypercalcemia → constipation, kidney stones, polyuria, and polydipsia.
 - ⇒ The pancreas is the second most commonly involved organ in MEN 1.
 - 60% of pancreatic endocrine tumours are gastrinomas (most common)
 →↑gastrin (Zollinger-Ellison syndrome) → recurrent peptic ulcers.
 - insulinoma → recurrent episodes of hypoglycemia, leading to confusion, dizziness, or loss of consciousness.
 - endoscopic ultrasound of the pancreas is the most sensitive modality for the detection of an insulinoma.
- The single most useful investigation to monitor patients with MEN 1 → Serum calcium
- Diagnosis → genetic testing
- Management
 - ⇒ Genetic screening for first-degree relatives
 - ⇒ Pituitary prolactinomas → cabergoline, a dopamine agonist
 - ⇒ Hyperparathyroidism → partial or total surgical parathyroidectomy
 - ⇒ Gastrinomas with peptic ulcer disease → proton pump inhibitor drugs.

MEN1 = three Ps

Pituitary, Parathyroid, Pancreas

Type 2 multiple endocrine neoplasia (MEN 2)

- MEN2A and MEN2B are both due to mutations in the gene RET. This is a protooncogene found on chromosome 10 that codes for a receptor tyrosine kinase.
- A gain-of-function mutation in the RET proto-oncogene makes it an oncogene, which
 causes the uncontrolled cell division seen in cancer.
- . MEN-2 is strongly associated with a family history of unexplained death in childbirth
- Subtypes
 - ⇒ MEN Type 2a
 - MEN type 2A includes two Ps and one M—parathyroid tumors and pheochromocytoma, combined with medullary thyroid carcinoma.
 - pheochromocytoma →↑catecholamines such as epinephrine →hypertension and often intermittent episodes of headaches, palpitation, pallor caused by vasoconstriction, and heavy sweating.
 - Medullary thyroid cancer often metastasized at presentation →hoarseness
 - Serum calcitonin levels should be obtained in the workup for medullary thyroid cancer.
 - young-onset hypertension with feature of hyperparathyroidism (↑ Ca & ↓
 P) → MEN Type 2a

⇒ MEN-2b

- MEN-2b present earlier than 2a
- MEN type 2B is associated with a single P and two Ms—pheochromocytoma, medullary thyroid carcinoma, and mucosal neuromas.
- Mucosal neuromas (benign tumors) develop in the mouth, eyes, and submucosa of almost all organs in the first decade of life and appear in 100% of patients with MEN2B (yellowish-white painless nodules on the lips or tongue, sclera, or eyelids).
- Marfanoid habitus → long limbs, wide arm span, and hyperlaxity of joints.

MEN2A = two Ps and one M

Parathyroid, Pheochromocytoma, Medullary thyroid carcinoma

MEN2B = one P and two Ms

Pheochromocytoma, Medullary thyroid carcinoma, Mucosal neuromas

- Diagnosis → genetic testing
- Management
 - □ Genetic screening for first-degree relatives
 - ⇒ All first-degree relatives who screen positive for the RET mutation should undergo prophylactic thyroidectomy given the very high risk of medullary thyroid cancer.
 - ⇒ For underlying phaeochromocytoma.
 - full alpha blockade with an agent such as phenoxybenzamine is essential
 - the most appropriate additional medication to control blood pressure is → phenoxybenzamine
 - Beta blockade without first alpha blocking raises the possibility of rebound hypertension due to unopposed action of the alpha vasoconstrictors; as such it is inadvisable to consider bisoprolol or atenolol.
 - The pheochromocytoma puts the patient at greatest risk, and therefore should be removed before other surgical procedures are performed.

 Annual testing of calcium and PTH from the age of 10 is recommended for child with family history of MEN-2

Which of the manifestations of MEN-2 has the most malignant potential? C cell hyperplasia

Which finding in a blood test will be the most characteristic in (MEN 2B) patient?

- Elevated metanephrines → phaeochromocytoma
- *Elevated Calcitonin* → Medullary thyroid cancer (used for *screening*, prognosis and *monitoring*)

Multiple endocrine neoplasia type II is due to mutation in which sort of receptor?

Membrane-bound tyrosine kinase receptor

What is the single most useful investigation to monitor patients with MEN 1? Serum calcium

Multiple endocrine neoplasia	
MEN 1	3 "P"s = Parathyroid, Pancreas, Pituitary gland
MEN 2A	1 "M", 2 "P"s = Medullary thyroid carcinoma, Pheochromocytoma,
MEN 2B	2 "M"s, 1 "P" = Medullary thyroid carcinoma, Marfanoid habitus/Multiple
	neuromas, Pheochromocytoma

<u>Autoimmune polyendocrinopathy syndrome (APS)</u> (<u>Polyglandular syndrome</u>)

Туре	Polyglandular syndrome type 1	Polyglandular syndrome type 2 Also called (Schmidt's disease)
inheritance	autosomal recessive caused by mutation of AIRE1 gene on chromosome 21	polygenic inheritance linked to HLA DR3/DR4.
Prevalence	Rare	More common
Age of presentation	Usually begins in childhood.	Usually begins in adult (most cases occurring between age 20 and 40 years)
Feature	Most common Mucocutaneous candidiasis (100%) (typically first feature as young child) Hypoparathyroidism (90%) Adrenal insufficiency (60%) Less common Other autoimmune diseases gonadal failure Primary hypothyroidism	Most common Adrenal insufficiency (100%) (the initial manifestation) Hypothyroidism Type-1 diabetes Less common Other autoimmune diseases Gonadal failure Diabetes insipidus (rare)
Diagnosis	2 out of 3 needed:	Patients have Addison's disease plus either: type 1 diabetes mellitus or autoimmune thyroid disease. No Hypoparathyroidism

• **Tryptophan hydroxylase autoantibodies** may be found in autoimmune polyendocrine syndrome associated with an autoimmune malabsorption.



Third edition

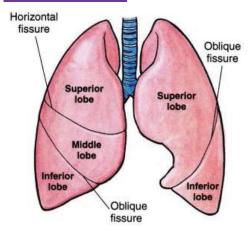
Notes & Notes

By Dr. Yousif Abdallah Hamad

Pulmonology

Updated 2022

Lung anatomy



Lung lobes

- Right lung has 3 lobes; Left has less lobes (2) and lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart
- The left lung have a part that the right lung does not have: the lingula, which is the homolog of the middle lobe of the right lung

Lung fissures

- The oblique fissure divides the superior and inferior lobes in the posterior aspect of both the right and left lungs
- · Horizontal fissure is found only in the right lung

Lung bronchi

- Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:
 - ⇒ While supine usually enters superior segment of right lower lobe.
 - ⇒ While lying on right side usually enters right upper lobe.
 - ⇒ While upright usually enters right lower lobe.
- Airway resistance highest in the large-to medium-sized bronchi and least in the terminal bronchioles

Cell types in respiratory zone

- Pseudostratified ciliated columnar cells are found in bronchi/early terminal bronchioles.
- Cuboidal cells are found in terminal bronchioles onward
- Simple squamous is the primary type of epithelium present in the alveoli

Anatomical land marks

- Cartilage and goblet cells extend to the end of bronchi.
- The Angle of Louis (also known as the sternal angle or Angle of Ludwig) corresponds
 to T4/T5 vertebral bodies, which is the location at which the trachea bifurcates to the
 main stem bronchi (carina).
- Structures perforating diaphragm:
 - ⇒ At T 8: IVC, right phrenic nerve
 - ⇒ At **T 10**: **oesophagus**, Vagus (CN10; 2 trunks)
 - ⇒ At T 12: aorta, thoracic duct, azygos vein.
- The trachea bifurcates at the level of T4 ("bi-four-cates at 4")
- Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Azygous lobe of the lung

- An azygos lobe is a normal variant that develops when a laterally displaced azygos vein creates a deep pleural fissure into the apical segment of the right upper lobe during embryological development.
- azygous lobe is seen in about 0.5% of routine chest X-rays and is a normal variant.
- The azygous lobe is formed when the posterior cardinal vein fails to migrate over the apex.
- It is seen as a 'reverse comma sign' behind the medial end of the right clavicle.

Top Tips

A patient aspirates vomit. Is the right or left lung a more common site for inhaled foreign bodies and why?

Right lung, because the right mainstem bronchus is wider, more vertical, and shorter than the left

A patient chokes on a peanut while upright. Where exactly in the lungs do you expect to find the peanut?

⇒ Right lower lobe

Diaphragmatic paralysis (Phrenic nerve palsy)

Innervation

• The diaphragm is innervated by the phrenic nerve (C3,4,5).

Causes

- Unilateral diaphragmatic paralysis (more common than bilateral)
 - ⇒ Trauma e.g. Thoracic surgery,
 - ⇒ Compression: cervical spondylosis, cervical compressive tumors
 - ⇒ viral infections (eq. Herpes zoster, poliomyelitis)
- Bilateral:
 - ⇒ Guillain-Barré
 - ⇒ Infection

Features

- Unilateral paralysis: usually asymptomatic
- Bilateral : dyspnoea may progress to ventilatory failure

Diagnosis of unilateral paralysis:

- suggested by asymmetric elevation of the affected hemidiaphragm on X-ray
- Spirometry (in the supine and sitting positions)
 - ⇒ The forced vital capacity (FVC) is ↓to 70 80 % of predicted and typically ↓↓
 decreases further by 15 to 25 % in the supine position.
- Confirmed by fluoroscopy
 - ⇒ by observing paradoxical diaphragmatic motion on sniff and cough
 - ⇒ During a forced inspiratory manoeuvre (the 'sniff test), the unaffected hemidiaphragm descends forcefully, increasing intra-abdominal pressure and pushing the paralysed hemidiaphragm cephalad (paradoxical motion)
 - ⇒ Fluoroscopy is inaccurate for the diagnosis of bilateral paralysis.

Treatment

- Unilateral diaphragmatic paralysis: do not require treatment.
- Bilateral: may require noninvasive positive pressure ventilation (NPPV), usually a bilevel positive airway pressure device (BPAP).

Lung physiology

Pulmonary surfactant

- · Surfactant is a mixture of phospholipids, carbohydrates and proteins
- · first detectable around 28 weeks of gestation
- Released by type 2 pneumocytes
- The main functioning component in surfactant is dipalmitoyl phosphatidylcholine (DPPC) or lecithin. which reduces alveolar surface tension.
- as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
- reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)

- lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration
- Because of surfactant, the pressure difference across the pleura required to inflate the lungs, is usually no more than about 4 cmH₂O.

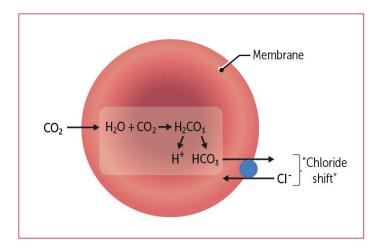
Pulmonary circulation

- The normal pulmonary circulation is characterised by:
 - 1. low pressures,
 - 2. low flow rates,
 - 3. high compliance vessels.
- Chronic hypoxic vasoconstriction may lead to pulmonary hypertension +/- cor pulmonale.
- A fall in the partial pressure of oxygen (pO2) in the blood causes a hypoxic
 vasoconstriction that shifts blood away from poorly ventilated regions of lung to wellventilated regions of lung and improves the efficiency of gaseous exchange.

Pulmonary arteries vasoconstrict in the presence of hypoxia

Chloride shift

- Cells metabolism → ↑CO2 → diffuses into RBCs → CO₂ + H₂O → carbonic anhydrase → carbonic acid (H₂CO₃) → HCO3- + H+
- . H+ combines with Hb
- HCO3- diffuses out of cell, CI- replaces it
- CO₂ produced in the periphery is converted into bicarbonate inside RBCs and then shifted out with chloride replacement



Bohr Effect

- Increasing acidity (or pCO2) means O2 binds less well to Hb
- High CO2 and H+ concentrations (from tissue metabolism) cause decreased affinity for O2 → O2 that is bound to Hb is released to tissue (the O2-Hb dissociation curve is shifted to the right).

Haldane effect

- ↑ pO2 means CO2 binds less well to Hb
- When Hb is oxygenated (in high pO2, for example, in the lungs):
- Oxygenated Hb has a decreased affinity for CO2 → CO2 that is bound to Hb is released in the pulmonary arteries to diffuse into the alveoli (the O2-Hb dissociation curve is shifted to the left).

Acclimatisation to life at high altitudes

- Acclimatisation results in increased Hb with erythrocytosis.
- Pulmonary artery pressure increases to oxygenate more blood.
- 2,3-DPG increases.
- Respiration is normal when subjects are acclimatised to altitude as is cardiac output. (Periodic respiration is a feature of non-acclimatisation).

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of ↑ compliance	Causes of ↓ compliance
Age	 Pulmonary edema
 Emphysema 	 Pulmonary fibrosis
	 Pneumonectomy
	Kyphosis

- Which part of the conducting zone of the respiratory tree has the least airway resistance?
 - ⇒ Terminal bronchioles

The cough center of the brain, located in the nucleus tractus solitarius of the medulla of the brainstem

Oxygen Dissociation Curve

Definition

- Oxygen Dissociation Curve describes the relationship between the percentage of saturated hemoglobin and partial pressure of oxygen in the blood.
- Each hemoglobin molecule has the capacity to carry four oxygen molecules.

Meaning of shifting the curve to the right or left

- Shifts to right = for given oxygen tension there is ↓ saturation of Hb with oxygen i.e. Enhanced oxygen delivery to tissues
- Shifts to left = for given oxygen tension there is ↑ saturation of Hb with oxygen i.e. ↓ oxygen delivery to tissues

Causes of shifting the curve to the right or left

oduses of shifting the curve to the right of left		
Shifts to R ight = R aised oxygen delivery (The R rule)	Shifts to Left = Lower oxygen delivery (The L rule)	
Raised [H+] (acidity)	Low [H+] (alkali)	
Raised PCO2	Low PCO2	
Raised 2,3-DPG	• Low 2,3-DPG	
Raised temperature	Low temperature	
	HbF, methemoglobin, carboxyhaemoglobin	

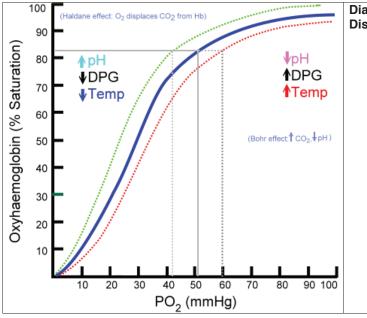


Diagram of Oxygen Dissociation Curve:

- Red line demonstrating shifting to the right.
- The green line demonstrating shifting to the left

The curve and Affinity

- Left shift of the curve is a sign of hemoglobin's ↑ affinity for oxygen (e.g. at the lungs).
- Similarly, right shift shows ↓ affinity, as would appear with an ↑ in body temperature, hydrogen ion, 2,3- diphosphoglycerate (2,3-DPG) or carbon dioxide concentration (the Bohr effect)
- Carbon monoxide has a much higher affinity for hemoglobin than oxygen does. In carbon monoxide poisoning, oxygen cannot be transported and released to body tissues thus resulting in hypoxia.

Top tips

Oxygen dissociation curve

- shifts Left Lower oxygen delivery Lower acidity, temp, 2-3
 DPG also HbF, carboxy/methaemoglobin
- shifts Right Raised oxygen delivery Raised acidity, temp, 2-3 DPG

Blood in the skeletal muscle is exposed to high temperatures, lower pH, and higher CO₂. The oxygen-hemoglobin dissociation curve shifts to the right, facilitating oxygen delivery to the tissue.

In the pulmonary vein, blood is exposed to a higher pH and lower CO₂. The oxygen-hemoglobin dissociation curve shifts to the left, facilitating oxygen binding to hemoglobin.

2,3-Diphosphoglycerate (2,3-DPG)

- 2,3-DPG is an important molecule made by tissue in response to a low pH and low oxygen environment.
- It may be helpful to think of 2,3-DPG as a help flag made by tissues in response to stress. When hemoglobin comes across higher 2,3-DPG, it "knows" that the tissue is in trouble and drops off extra oxygen. Therefore, as 2,3-DPG increases, the binding affinity of oxygen for hemoglobin decreases, which results in a rightward shift of the dissociation curve.

Question

A 24-year-old woman is evaluated before and after practice to assess oxygen delivery to her muscles. The hemoglobinoxygen dissociation curve is shown.

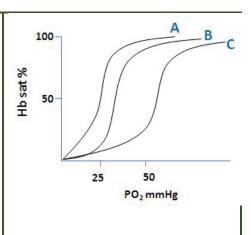
Curve B is taken before practice.

Which characteristics will most probably describe curve A?

Answer:

If curve B is taken before practice, it will be used as reference point. Curve A shows shifts to the left.

Increased pH with decreased 2,3-diphosphoglycerate concentration



Pulmonary function tests

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive.

Normal lung volumes

Normal lung volumes			
	Definition	Normal range	
Total lung capacity (TLC)	Volume of air in the lungs after maximal inhalation [= vital capacity + residual volume].	6–6.5 L	
Vital capacity (VC)	Maximum volume of air that can be expired after a maximal inspiration. [] with age]	4.5–5 L	
Residual volume (RV)	Volume of air that remains in the lungs after maximal exhalation.[† with age & obstructive lung disease]	1–1.5 L	
Tidal volume (TV)	Volume of air that is inhaled and exhaled in a normal breath at rest	~ 500 mL or 7 mL/kg	
Inspiratory reserve volume	Maximum volume of air that can still be forcibly inhaled following the inhalation of a normal TV	3–3.5 L	
Inspiratory capacity (IC)	Maximum volume of air that can be inhaled after the exhalation of a normal TV. [IC = TV + IRV]	3.5–4 L	
Expiratory reserve volume (ERV)	Maximum volume of air that can still be forcibly exhaled after the exhalation of a normal TV	1.5 L	
Expiratory capacity (EC)	Maximum volume of air that can be exhaled after the inspiration of a normal TV	2 L	
Functional residual capacity (FRC)	Volume of air that remains in the lungs after the exhalation of a normal TV	2.5–3 L	
Dead space	areas of the lung not involved in gas exchange. Anatomic dead space includes the non- respiratory airways and exists in all healthy lungs. Physiologic dead space includes the anatomic dead space plus any alveoli that are not perfused and thus cannot participate in gas exchange	150 ml	

Obstructive vs. Restrictive lung diseases

	Obstructive	Restrictive
Spirometry	FEV1/FVC <0.7 (<70%)	FEV1/FVC >0.7 (> 70%)
	FEV1 - significantly reduced (<80% predicted normal)	FEV1 - reduced (<80% predicted normal)
	FVC - reduced or normal FEV1% (FEV1/FVC) - reduced	FVC - significantly reduced (<70% predicted normal) FEV1% (FEV1/FVC) - normal (>0.7) or increased

	Obstructive	Restrictive
Examples	Chronic obstructive pulmonary disease	Intrapulmonary idiopathic pulmonary fibrosis extrinsic allergic alveolitis coal worker's pneumoconiosis/progressive massive fibrosis silicosis sarcoidosis histiocytosis drug-induced fibrosis: amiodarone, bleomycin, methotrexate asbestosis Extrapulmonary neuromuscular disease: polio, myasthenia gravis obesity scoliosis

Forced vital capacity (FVC)

- A measure of the force, volume, and speed with which air can be maximally expelled from the lungs.
- The maneuver would be to take a deep breath, and then blow it out as hard as you can for as long as you can to maximally expel air from the lungs.
- Indications
 - commonly done to assess patients with asthma and chronic obstructive pulmonary disease.
 - the best way to monitor respiratory function in any neurological disorders that can affect the respiratory muscles (e.g. GBS, myasthenia gravis). ITU admission is recommended when FVC is less than 20 mL/kg and intubation is recommended in most cases when FVC is less than 15 mL/kg.

Peak expiratory flow rate (PEFR)

- **Definition**: The maximum airflow rate attained during forced expiration.
- Normal values
 - ⇒ PEF values are usually expressed as L/min; when measured as part of spirometry, values are expressed in L/sec. To convert, multiply L/sec x 60 sec/min = I /min.
 - ⇒ Peak flow meters are handheld devices used to measure PEFR in the ambulatory setting
 - ⇒ Normally : ≥ 80% of the predicted average value
 - ⇒ Dependent upon factors such as gender, age and height. The most accurate correlation of the peak expiratory flow rate (PEFR) is with height. PEFR is typically higher in males than females and higher in taller patients.

Advantages

- ⇒ It is effort-independent.
- ⇒ In patients with asthma, the PEFR % predicted correlates reasonably well with the FEV₁ and provides an objective measure of airflow limitation when spirometry is not available

 \Rightarrow

Disadvantages

- ⇒ predominantly assesses large airway caliber and can underestimate the effects of asthma in the small airways.
- ⇒ Restrictive processes that limit full inspiration, such as chest wall disease, obesity, and muscle weakness, can lead to a reduced PEF in the absence of airflow limitation. Thus, values for PEF that are less than 80 percent of predicted should be further evaluated with spirometry before assuming that the abnormality is due to asthma.

The differences between Peak Flow Meters and Spirometry

Peak Flow Meter	Spirometry
 ⇒ Measures ability to exhale ⇒ Will vary with lung capacity ⇒ Use with charts to detect OBSTRUCTIVE disease ⇒ Can be used by patients to monitor lung 'function' 	 ⇒ Simultaneous measurement of flow and capacity ⇒ Can be used to diagnose both OBSTRUCTIVE and RESTRICTIVE disease (gold standard) ⇒ Costs more than peak flow meters
artifiliante.	

Flow-volume loop

- provides additional information about the location of airway constriction
- Best test for upper way obstruction. the upper airway is defined as that portion of the airway extending from the mouth to the mainstem bronchi

Explanation of high FEV-1/FVC ratio in lung fibrosis

Lung fibrosis → ↑↑high elastic recoil → most forced expiratory volume (FEV-1) will be expelled in the first second compared to full forced expiration → a relatively high FEV-1/FVC ratio.

Obesity → extra-thoracic restriction

• Obesity could show a significant restrictive defect.

Patients with respiratory muscle weakness show spirometric findings of restrictive lung disease.

- What is the best pre-operative screen of pulmonary function for a smoker patient evaluated for a coronary artery bypass graft (CABG).?
 - ⇒ Ratio of the forced expiratory volume in 1 second to the forced vital capacity

Flow volume loop is the investigation of choice for upper airway compression

<u>Transfer factor</u> (D_{LCO} or T_{LCO} (<u>diffusing capacity</u> or transfer factor of the <u>lung</u> for <u>carbon monoxide</u> (CO))

- The transfer factor describes the rate at which a gas will diffuse from alveoli into blood.
- Carbon monoxide is used to test the rate of diffusion.
- Results may be given as the total gas transfer (DLCO, T_{LCO}) or that corrected for lung volume (transfer coefficient, KCO).
- Diffusion capacity of carbon monoxide depends on the thickness of the alveolar wall.
 diffusion will be increased in healthy compared with unhealthy lungs, where the
 thickness is likely to increase and the surface area available for gas exchange to
 decrease.

Diffusing capacity of the lungs for carbon monoxide (DLCO) (also known as transfer factor for carbon monoxide or TLCO)

- DLCO measures the ability of the lungs to transfer gas from inhaled air in the alveoli to the red blood cells in pulmonary capillaries.
- · Used to identify the cause of dyspnea or hypoxemia,

Factors interfere with interpretation of the Diffusing capacity (DLCO) test

- Smoking
 - ⇒ patients should avoid cigarette smoking on the day of the test
 - ⇒ Carbon monoxide in cigarette smoke → ↑ carboxyhaemoglobin (COHb) (to as high as 10-15% (normal value 1-2%) → ↓ DLCO. Increasing COHb reduces DLCO
- Supplemental oxygen
 - ⇒ discontinue any supplemental oxygen for at least 15 minutes prior to testing.
- Significant amount of Alcohol in the morning of the test (not small amount)
- Severe kyphosis (not mild)
- Sever scoliosis (not mild)

Causes of raised and lower DLCO

 Where alveolar haemorrhage occurs, the DLCO tends to increase due to the enhanced uptake of carbon monoxide by intra-alveolar haemoglobin.

Causes of a raised DLCO	Causes of a lower DLCO
Asthma Pulmonary haemorrhage (Wegener's, Goodpasture's) Left-to-right cardiac shunts Polycythaemia Hyperkinetic states Early left heart failure Male gender Exercise Obesity	Pulmonary fibrosis Pneumonia Pulmonary emboli Pulmonary oedema Emphysema bronchiolitis obliterans Anaemia Low cardiac output Pulmonary AV malformations carboxyhemoglobinemia. hepatopulmonary syndrome lymphangioleiomyomatosis

 Transfer factor (DLCO) and transfer co-efficient (KCO) can be normal or elevated in patients with asthma but are always reduced in emphysema.

- Pulmonary AV malformations cause right-to-left shunts, so reducing Tlco values and provoking hypoxaemia (\perp Pao2), with a normal lung volumes (eg FEV1 & FVC).
- Low DLCO combined with reduced lung volumes suggests interstitial lung disease.
- Normal DLCO associated with low lung volumes suggests
 → an extrapulmonary cause of the restriction, such as pleural effusion, pleural thickening, neuromuscular weakness, or kyphoscoliosis.

Top Tips

Transfer factor

- · raised: asthma, haemorrhage, left-to-right shunts, polycythaemia
- · low: everything else

Transfer coefficient of carbon monoxide (KCO)

Overview

- The transfer coefficient (Kco) represents the uptake of carbon monoxide per litre of effective alveolar volume (Va)
- KCO is a measure of the efficiency of gas exchange into the blood stream.

Causes of reduced Kco: (It is reduced if the lungs are damaged)

- Restrictive lung disease e.g. Interstitial lung disease
 - ⇒ the best test after CT- to confirm restrictive lung disease due to a parenchymal disorder
 - Normal KCO may rule out significant restrictive lung disease
- Sarcoidosis would reduce the transfer coefficient as there is damage to the alveolar cells themselves

Causes of an increased Kco

- Increased if there is additional blood in the lungs to remove carbon monoxide (e.g. †blood flow, haemorrhage, or polycythaemia).
- Extrapulmonary volume restriction
 - ⇒ density of pulmonary capillaries is unusually high in relation to the (restricted) lung volume at which the measurement is made.
- · increase with age.

Causes of an increased KCO with a normal or reduced TLCO

- Low TIco but normal/high Kco (ie the same cardiac output is going through a smaller alveolar volume) is characteristic of extra-thoracic restriction:
 - ⇒ pneumonectomy/lobectomy
 - ⇒ scoliosis/kyphosis
 - ⇒ neuromuscular weakness
 - ⇒ ankylosis of costovertebral joints e.g. ankylosing spondylitis
 - ⇒ Severe thoracic skin thickening,
 - ⇒ Pleural disease, extensive bilateral pleural thickening
- In intrapulmonary restriction, both (TIco & Kco) are usually decreased.

 Isolated decreases in gas transfer are typical of pulmonary vascular diseases such as vasculitis and recurrent pulmonary embolism.

Relation between DLco, VA (alveolar volume) & KCO (transfer coefficient)

- Dlco is simply the product of Va and Kco
- TLCO = KCO x Alveolar volume (VA)

Arterial Blood Gas (ABG)

Arterial blood gases should be used for assessing respiratory failure in Critically ill Patients or those with Shock or Hypotension (Systolic blood pressure < 90mmHg)

(British Thoracic Society, 2017)

Reference ranges

• PaCO2: 35-45 mm Hg

SaO2: ≥ 95%pH: 7.35–7.45

HCO3-: 21 to 27 mEg/L

• Resting PaO2 > 80 mm Hg is considered normal.

Procedure

 A modified Allen test must be performed before the radial artery is punctured to assess collateral circulation in the hand.

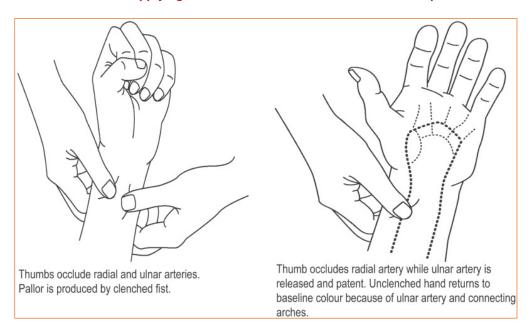
Contra-Indications of ABG sampling

- Absent ulnar circulation as demonstrated by Modified Allen's Test.
- Impaired circulation e.g. Raynaud's Disease
- History of arterial spasms
- Distorted anatomy/ arteriovenous fistula trauma/burns to the limb at or proximal to the attempted arterial puncture site
- · Medium or high dose anticoagulation therapy, or history of clotting disorder
- Severe coagulopathy
- Abnormal or infectious skin processes at/or near puncture site

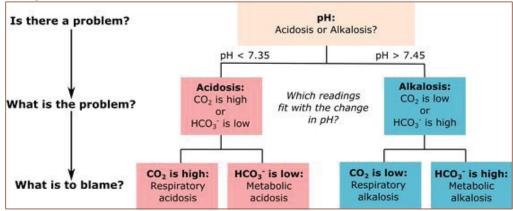
Modified Allen's test

- modified Allen test measures arterial competency, and should be performed before taking an arterial sample.
 - ⇒ Ask the patient to clench his fist; if the patient is unable to do this, close the person's hand tightly.
 - ⇒ Using your fingers, apply occlusive pressure to both the ulnar and radial arteries, to obstruct blood flow to the hand.
 - ⇒ While applying occlusive pressure to both arteries, have the patient relax his hand, and check whether the palm and fingers have blanched. If this is not the case, you have not completely occluded the arteries with your fingers.
 - ⇒ Release the occlusive pressure on the ulnar artery only to determine whether the modified Allen test is positive or negative.
 - If the hand flushes within 5-15 seconds it indicates that the ulnar artery has good blood flow → positive test.

If the hand does not flush within 5-15 seconds, it indicates that ulnar circulation is inadequate or nonexistent; in this situation, the radial artery supplying arterial blood to that hand should not be punctured.



Interpretation of ABG



- Hypoxemic respiratory failure (type 1 respiratory failure):
 ↓ PaO2
- Hypercapnic respiratory failure (type 2 respiratory failure): ↑ PaCO2 and ↓ PaO2
- Mixed metabolic and respiratory acidosis
 - \Rightarrow pH \rightarrow below 7.35
 - \Rightarrow PCO₂ \rightarrow elevated (> 6 kP_a) indicating a respiratory cause for acidosis
 - ⇒ Bicarbonate → reduced (< 20 mmol/L) which is contributing to the acidosis.
 - ⇒ the most likely biochemical imbalance seen in fluid inhalation is → Mixed metabolic and respiratory acidosis
 - inhalation of fluid → disordered gas exchange → respiratory acidosis.

- Metabolic acid results from intravascular volume depletion, hypotension and consequent tissue hypoxia.
- Compensated respiratory acidosis \rightarrow normal PH, high CO₂, low O₂.
 - ⇒ The fact that the pH is normal means that there must be bicarbonate retention to compensate.
 - ⇒ In bronchopulmonary dysplasia, there is usually long-term CO₂ retention with compensatory increase in bicarbonate leading to a positive base excess and normal pH.
- Pathophysiological changes in case of acute acidosis:
 - Occurred too quickly for metabolic compensation to occur via renal bicarbonate reabsorption, which takes 3-5 days to occur. (bicarbonate will be normal in acute respiratory acidosis)
 - ⇒ The oxygen dissociation curve is shifted to the right in acute acidosis, i.e. haemoglobin has a decreased affinity for oxygen.
 - ⇒ High pulmonary pressures would be expected after arrest scenario, as the pulmonary arterioles constrict in response to hypoxia.

Chest_x-ray

Differential diagnosis of cavitating lung lesion

- abscess (Staph aureus, Klebsiella and Pseudomonas)
- · squamous cell lung cancer
- tuberculosis
- Wegener's granulomatosis
- Progressive massive fibrosis: is a complicated coal worker's pneumoconiosis where pulmonary nodules coalesce and cavitate.
- · pulmonary embolism
- Systemic embolisation: occurs in 20-50% of cases of infective endocarditis, and can involve the lungs, central nervous system, coronary arteries, spleen, bowel and extremities.
- · rheumatoid arthritis
- aspergillosis, histoplasmosis, coccidioidomycosis
- Actinomycosis: is a chronic granulomatous disorder caused by a Gram-positive anaerobe.

Differential diagnosis of diffuse opacities on chest X-ray

- Pulmonary oedema
- Interstitial lung disease
- Vasculitic lung disease
- Pulmonary haemorrhage

Coin lesions on chest x-ray

- Coin lesions (solitary pulmonary nodule)
 - ⇒ malignant tumour: lung cancer or metastases
 - ⇒ benign tumour: hamartoma
 - ⇒ infection: pneumonia, abscess, TB, hydatid cyst
 - ⇒ AV malformation

White lung lesions on chest x-ray

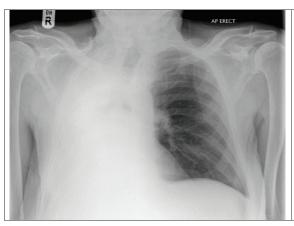
- · causes of white shadowing in the lungs including:
 - consolidation
- pneumonectomy
- pleural effusion
- · specific lesions e.g. tumours

collapse

- fluid e.g. pulmonary oedema
- If there is a 'white-out' of a hemithorax it is useful to assess the position of the trachea is it central, pulled or pushed from the side of opacification.

Trachea pulled toward the white-out	Trachea central	Trachea pushed away from the white-out
Pneumonectomy Complete lung collapse (Atelectasis) e.g. endobronchial intubation Pulmonary hypoplasia	Consolidation Pulmonary oedema (usually bilateral) Mesothelioma	Pleural effusion Diaphragmatic hernia Large thoracic mass

- In the context of an acute aspiration, the most likely process is atelectasis secondary to bronchial obstruction.
- Obstruction of the mainstem bronchus will prevent gas from entering the affected lung and will lead to the collapse of that lung.
- The collapsed lung will cause complete whiteout of the hemithorax on chest X-ray and will cause ipsilateral tension on the mediastinum leading to shifting of the trachea toward the affected lung.



Lung collapse

- note how the trachea is pulled towards the side of the white-out

Characteristics of consolidation on chest x-ray

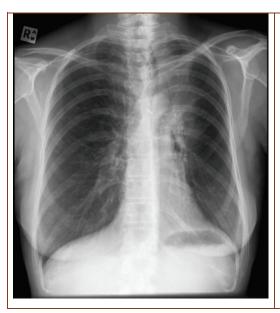
- Consolidation in the left lower lobe → obliterates the diaphragm.
- Lingular consolidation → obliterate the left heart border.
- Consolidation of the right middle lobe → obscures the right heart border (right atrial edge). More extensive consolidation also involves the right and left peri-hilar regions. The superior extent is well demarcated, due to the horizontal fissure.

- Right upper lobe collapse results in → displacement of the horizontal fissure upwards.
 The right hilum can also appear enlarged.
 - ⇒ The classical signs of right upper lobe consolidation → abnormal opacity within the right upper lobe abutting the horizontal fissure.

The loss of the left heart border is a classic sign of left lingual consolidation.

Lobar collapse on chest x-ray (Atelectasis)

- Signs of lobar collapse on a chest x-ray
 - ⇒ tracheal deviation towards the side of the collapse
 - ⇒ mediastinal shift towards the side of the collapse
 - ⇒ elevation of the hemidiaphragm
- Causes
 - ⇒ lung cancer (the most common cause in older adults)
 - ⇒ foreign body
 - ⇒ mucous plugging (e.g. in cystic fibrosis, post-operative complication, asthma)
 - Treatment
 - adequate hydration and chest physiotherapy.
 - Bronchoscopy with lavage may be required if this is unsuccessful.



This patient has a **left upper lobe collapse**. The following can be seen on the film to support this:

- hazy opacity projected over the left upper zone
- · deviation of the trachea to the left
- elevation of the left hemidiaphragm
- loss of lung volume in the left hemithorax



Lung collapse (Atelectasis)

 There is increased opacity in the right upper zone, The lateral / inferior border of the shadowing actually represents the horizontal fissure which has been 'dragged' upwards.

Pleural calcification

Unilateral pleural calcification

- most commonly occurs as a chronic change secondary to:
 - ⇒ pleural infection: tuberculous empyema, pyogenic empyema,
 - ⇒ haemothorax (post-traumatic)

Bilateral pleural calcification

- Common
 - ⇒ calcified pleural plaques are usually considered asbestos-related.
- Other rarer causes
 - ⇒ radiation exposure,
 - ⇒ hyperparathyroidism,
 - ⇒ pulmonary infarction,
 - ⇒ pancreatitis.

Solitary pulmonary nodules

Definition

- A small (≤30 mm), well defined lesion completely surrounded by pulmonary parenchyma detected as an incidental finding, either on chest x-ray or CT scans.
- Lesions larger than 3 cm are considered masses and are treated as malignancies until proven otherwise.

Causes

- benign nodules (The most common)
 - Infectious granulomas and hamartomas are the most common causes of benign nodules.
- malignant nodules
 - ⇒ The most common causes of malignant nodules are primary lung cancer, lung metastases, and carcinoid tumors.

Management

- Risk stratification of incidental pulmonary nodules
 - ⇒ consider the risk factors for lung cancer or metastases, as well as size and character of the nodule.
 - ⇒ surveillance according to British Thoracic Society Guidelines published in 2005.
 - Nodules < 5 mm require no further surveillance.
 - Nodules 5-6mm require CT at 1 year
 - Nodules 6-8 mm require CT at 3 months
 - Nodules > 8 mm require malignancy risk calculation using the Brock model and should then have CT or PET according to whether this risk is > 10%.
 - To determine risk of malignancy following CT the BTS uses the Brock model
 - The Brock model considers age, gender, family history and features of the nodule
 - Only nodules which are greater than 8mm in diameter and have a greater than 10% risk of malignancy, as assessed by the Brock model (this can be accessed on the BTS website) should undergo PET-CT and then, based on outcomes, be assessed for obtaining a histological sample.
- Requesting a previous chest x-ray is the most appropriate first step in management
 of a patient with a solitary pulmonary nodule, especially when the risk of malignancy is
 high (age > 40 years, history of smoking).
 - ⇒ If there are no new changes, the patient can be followed-up with yearly chest x-rays.
 - ⇒ However, if there are new changes noted (additional nodules, enlargement), or no previous chest x-ray is available, a CT scan is indicated to assess for nodule size, location, and signs of malignancy, before eventual biopsy.

Alveolar-arterial (A-a) oxygen gradient

Definition

The difference between the partial pressure of oxygen in the alveoli (A) and the partial
pressure of oxygen in the arteries (a).

Indications of uses

- Used in diagnosing the source of hypoxemia. For example,
 - ⇒ in high altitude, the arterial oxygen PaO₂ is low but only because the alveolar oxygen (PAO₂) is also low.
 - ⇒ in states of ventilation perfusion mismatch, such as pulmonary embolism or rightto-left shunt, oxygen is not effectively transferred from the alveoli to the blood which results in elevated A-a gradient
- in hypoxaemia it can differentiate between extrinsic and intrinsic restrictive lung disease
 - ⇒ if A-a gradient is normal → the cause is extrinsic, so exclude intrinsic lung disease

Normal range

- The normal range varies with age, altitude, and the concentration of inhaled oxygen.
 Normal range for a young person breathing room air at sea level is 5–10 mm Hg and increases with physical exercise.
- A-a gradient = alveolar O2 (PAO2) arterial O2 (PaO2)

Causes of increased A-a gradient

- Age
- Higher concentration of inhaled oxygen
- Right-to-left shunting (e.g. cyanotic heart disease)
- Fluid in alveoli: e.g., CHF, ARDS, pneumonia
- Ventilation/perfusion (V/Q) mismatch (due to increased dead space or shunting): e.g., pulmonary embolism, pneumothorax, atelectasis, obstructive lung disease, pneumonia, pulmonary edema
- Alveolar hypoventilation: interstitial lung disease, lung fibrosis (usually manifests with

 CO2)

Causes of hypoxaemia with normal A-a gradient

- high altitude (both PAo2 and Pao2 are equally reduced)
- hypoventilation (except lung):
 - ⇒ higher respiratory centre (e.g. drug induced)
 - ⇒ upper air way (e.g. acute epiglottitis)
 - ⇒ chest wall (e.g. kyphoscoliosis)
 - ⇒ respiratory muscles (e.g. myasthenia graves)
 - ⇒ haemoglobin defect
 - anaemia : normal paO2 , normal SaO2 , low O2 content
 - methemoglobinemia : normal PaO2, low SaO2 , low O2 content

An increased A-a gradient may occur in hypoxemia due to shunting, ventilation-perfusion mismatch, or impaired gas diffusion across the alveoli due to fibrosis or edema.

The A-a gradient remains normal with hypoventilation due to CNS and neuromuscular disorders (no diffusion defect) and in high altitude (despite a lower fraction of inhaled O2).

Finger clubbing

Definition

- Loss of the natural angle between the nail and the nail bed.
- increased curvature of the nail.

Causes

- Suppurative diseases:
 - ⇒ long-standing bronchiectasis
 - ⇒ acute lung abscesses
 - ⇒ empyema
- Malignant disease especially carcinoma of the bronchus and pleural malignancy
- Fibrosing alveolitis
- Asbestosis
- hypertrophic pulmonary osteoarthropathy,
 - ⇒ painful osteitis of the distal ends of the long bones of the lower arms and legs.
 - ⇒ Malignancy is associated in 95% of these cases.

Finger clubbing is not seen in uncomplicated bronchitis.

Respiratory failure



Respiratory failure

- Type 1 → hypoxaemia (P_aO₂ < 8.0 kPa) without hypercapnia (P_aCO₂ normal or decreased (<6.0 kPa)
- Type 2 → Hypoxemia (PaO2 <8kPa) with hypercapnia (PaCO2 >6.0kPa).

Type 2 respiratory failure with normal CXR → neuromuscular weakness

Type 1 respiratory failure

- Definition
 - hypoxaemia (P_aO₂ < 8.0 kPa) without hypercapnia (P_aCO₂ normal or decreased (<6.0 kPa)
 - ⇒ Causes:
 - Low ambient oxygen (e.g. at high altitude)
 - Ventilation-perfusion mismatch (parts of the lung receive oxygen but not enough blood to absorb it, e.g. pulmonary embolism)
 - Alveolar hypoventilation (decreased minute volume due to reduced respiratory muscle activity, e.g. in acute neuromuscular disease); this form can also cause type 2 respiratory failure if severe
 - Diffusion problem (oxygen cannot enter the capillaries due to parenchymal disease, e.g. in pneumonia or ARDS)
 - Shunt (oxygenated blood mixes with non-oxygenated blood from the venous system, e.g. right-to-left shunt)

Type 2 respiratory failure

- Definition: Hypoxemia (PaO2 <8kPa (60 mmHg)) with hypercapnia (PaCO2 >6.0kPa (45 mmHg)).
- Causes:
 - ⇒ Increased airways resistance (COPD, asthma, suffocation)
 - ⇒ Reduced breathing effort → hypoventilation:
 - acutely due to drug overdose and brain stem lesion
 - chronically due to: gross obesity, kyphoscoliosis (and similar musculoskeletal disorders)
 - Hypoventilation, where inadequate alveolar ventilation results in low alveolar PO₂, is the only cause of hypoxia that inevitably causes raised PaCO₂.
 - ⇒ A decrease in the area of the lung available for gas exchange (such as in chronic bronchitis)
 - ⇒ Neuromuscular problems (respiratory muscle weakness) (Guillain-Barre syndrome, motor neuron disease)
 - ⇒ Deformed (kyphoscoliosis), rigid (ankylosing spondylitis), or flial chest.

 \Rightarrow

Bronchial Asthma

Immunological response involved in atopic asthma:

- Immediate response: type I hypersensitivity
 - ⇒ immunomodulators involved: mast cells, histamine
 - ⇒ Result in immediate bronchoconstriction reaction
 - ⇒ Usually subsides within two hours
 - ⇒ Reversible with bronchodilators.
- · Late phase:
 - ⇒ type IV hypersensitivity response
 - ⇒ Results in bronchoconstriction, airways inflammation, hyper-responsiveness and oedema.
 - ⇒ This typically occurs three to12 hours after the immediate response
 - ⇒ Less susceptible to bronchodilators.

Pathogenesis of asthma:

- Asthma occurs due to a combination of airway hyper-responsiveness, airflow limitation and airway inflammation
- The alveolar functional structure is preserved in asthma.

Near fatal asthma

- The British Thoracic Society defines near fatal asthma as an attack with raised PaCO₂ and/or requiring mechanical ventilation with raised inflation pressures.
- A raised PaCO₂ is an important sign that intubation may be required if the patient is not responding to maximum medical management.

Features

- wheeze, cough or breathlessness, and any daily or seasonal variation in these symptoms, any triggers that make symptoms worse
- a personal or family history of atopic disorders.

Asthma diagnosis (NICE guidelines 2017)

NICE guidelines
Do not use symptoms alone without an objective test to diagnose asthma.
Empirically inhaled corticosteroids may affect the results of spirometry and
FeNO tests

- Step 1: Exclude occupational asthma by asking if their symptoms are better on days away from work/during holidays.
- Step 2: Test for airway inflammation → Fractional exhaled nitric oxide (FeNO) test
 ⇒ If > 40 ppb → positive
- Step 3: test for obstructive airway disease → Spirometry
 - ⇒ FEV1/FVC ratio < 70% → positive (obstructive spirometry).
- Step 4: test for Bronchodilator reversibility (BDR) → bronchodilators + Spirometry
 - ⇒ improvement in FEV1 ≥ 12%, + ↑ volume ≥ 200 ml → positive

- Step 5: If there is diagnostic uncertainty (e.g. positive BDR with borderline FeNO OR obstructive spirometry + negative BDR) → Peak expiratory flow variability for 2 to 4 weeks ⇒ value ≥ 20% variability is a positive test.
- Step 6: If there is diagnostic uncertainty (positive FeNO ≥ 40 BUT normal spirometry and no variability in peak flow readings OR borderline FeNO with obstructive spirometry BUT negative BDR and no variability in peak flow readings) → Airway hyperreactivity measures → Direct bronchial challenge test with histamine or methacholine

⇒ PC20 value ≤ 8 mg/ml is a positive test.

NICE quality statement: Adults with new onset asthma are assessed for occupational causes.

- Are you better on days away from work?
- Are you better on holiday?

All patients with suspected B. Asthma should have spirometry with a bronchodilator reversibility (BDR) test and FeNO test

Diagnosis of asthma (NICE guidelines 2017) Patients ≥ 17 years: Exclude occupational asthma (by asked if their symptoms are better on days away from work/during holidays). Do spirometry with a bronchodilator reversibility (BDR) test + Fractional exhaled nitric oxide (FeNO) for all patients □ obstructive spirometry → FEV1/FVC ratio < 70% </p> positive BDR test → improvement in FEV1 ≥ 12%, together with an increase in volume ≥ 200 positive FeNO test ≥ 40 monitor Peak expiratory flow variability: for 2 to 4 weeks, if there is diagnostic uncertainty: normal spirometry OR □ obstructive spirometry, positive BDR but a FeNO ≤ 39 ⇒ Regard a value > 20% variability as a positive test. Patients 5-16 years: Do spirometry with a bronchodilator reversibility (BDR) test Do a FeNO test if there is: normal spirometry OR obstructive spirometry with a negative BDR test

In asthma diagnosis:

Positive spirometry with a bronchodilator reversibility (BDR) test → improvement in FEV1 of ≥12%

⇒ Regard a value of FeNO test ≥ 35 as a positive test.

Positive peak flow meter → > 20% variation

Positive tests in Asthma		
Test	Positive result	
Fractional exhaled nitric oxide (FeNO)	40 ppb or more	
FeNO	35 ppb or more	
Obstructive spirometry	Forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio less than 70% (or below the lower limit of normal if this value is available)	
Bronchodilator reversibility (BDR) test	Improvement in FEV1 of 12% or more and increase in volume of 200 ml or more	
BDR test	Improvement in FEV1 of 12% or more	
Peak flow variability	Variability over 20%	
Direct bronchial challenge test with histamine or methacholine	Provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) of 8 mg/ml or less	

Management of asthma (NICE guidance 2017).

One of the key changes is in 'step 3' - patients on a SABA + ICS whose asthma is not well controlled should be offered a leukotriene receptor antagonist, not a LABA

Step	Notes
1	Short-acting beta agonist (SABA)
Newly-diagnosed asthma	
Not controlled on previous step OR Newly-diagnosed asthma with symptoms ≥ 3 / week or night-time waking	SABA + low-dose inhaled corticosteroid (ICS)
3	SABA + low-dose ICS + leukotriene receptor antagonist (LTRA)
4	SABA + low-dose ICS + long-acting beta agonist (LABA) Continue LTRA depending on patient's response to LTRA
5	SABA +/- LTRA

	Switch ICS/LABA for a maintenance and reliever therapy (MART), that includes a low-dose ICS	
6	SABA +/- LTRA + medium-dose ICS MART OR consider changing back to a fixed-dose of a moderate-dose ICS and a separate LABA	
7	SABA +/- LTRA + one of the following options: increase ICS to high-dose (only as part of a fixed-dose regime, not as a MART) a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) seeking advice from a healthcare professional with expertise in asthma	

Drugs used in asthma

Drug	Mechanism of action	Notes
Salbutamol	Beta receptor agonist	 Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle through effects on beta 2 receptors Used in asthma and chronic obstructive pulmonary disease (COPD). Salmeterol has similar effects but is long-acting
Corticosteroids	Anti-inflammatory	 Inhaled corticosteroids are used as maintenance therapy Oral or intravenous corticosteroids are used following an acute exacerbation of asthma or COPD
Ipratropium	Blocks the muscarinic acetylcholine receptors	Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle Used primarily in COPD Tiotropium has similar effects but is long-acting
Methylxanthines (e.g. theophylline)	Non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP	Given orally or intravenously Has a narrow therapeutic index
Montelukast, zafirlukast	Blocks leukotriene receptors	Usually taken orally Useful in aspirin-induced asthma

Steroid inhalation

- Fluticasone is more lipophilic and has a longer duration of action than beclomethasone
- Hydrofluoroalkane is now replacing chlorofluorocarbon as the propellant of choice.
 - ⇒ Only half the usual dose is needed with hydrofluoroalkane due to the smaller size of the particles
- Table showing examples of inhaled corticosteroid doses
- _

Dose	Example
low dose	≤ 400 micrograms budesonide or equivalent
moderate dose	400 micrograms - 800 micrograms budesonide or equivalent
high dose	> 800 micrograms budesonide or equivalent

Side effects:

- \Rightarrow Inhaled corticosteroids $\rightarrow \downarrow \downarrow$ skin collagen synthesis \rightarrow skin fragility $\rightarrow \uparrow \uparrow$ tendency for bruising & vascular changes
- □ Cushing's syndrome: Interaction with potent cytochrome P450-3A4 inhibitor → elevations in plasma fluticasone concentrations (even nasal or inhaled preparations) → suppress endogenous cortisol levels and produce Cushing's syndrome. eg: a patient with HIV and asthma, C/O tiredness, lethargy and weight gaining → suspect Cushing's syndrome produced by Ritonavir, a protease inhibitor which is an extremely potent cytochrome P450-3A4 inhibitor.

Long acting B2-agonists

- Action:
 - ⇒ acts as bronchodilators but also inhibit mediator release from mast cells.
 - ⇒ The duration of action of salmeterol is around 12 hours
- Side effects: Salmeterol → may cause paradoxical bronchospasm

Leukotriene receptor antagonists

- Action
 - ⇒ Montelukast, zafirlukast
 - CysLT1 antagonist; it blocks the action of leukotriene on cysteinyl leukotriene receptor CysLT1 by binding to it.
 - ⇒ Zileuton → blocks leukotriene synthesis by inhibiting 5-lipoxygenase,
 - inhibits 5-lipoxygenase pathway, blocking the conversion of arachidonic acid to leukotrienes.
 - ⇒ have both anti-inflammatory and bronchodilatory properties
- Inductions
 - ⇒ should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting b2-agonist
 - ⇒ have been shown to be as effective as doubling the dose of inhaled steroid.
 - ⇒ asthma with allergic rhinitis
 - ⇒ aspirin-induced asthma
 - ⇒ exercise-induced asthma
- Side effects
 - ⇒ associated with the development of Churg-Strauss syndrome

Asthma drugs: leukotriene inhibitor action:

- ⇒ Zafirlukast → Inhibitor of LT receptor
- ⇒ Zileuton → Antagonist of lipoxygenase

Omalizumab

- Action: monoclonal antibody that binds to IgE.
- **Indications:** severe refractory, persistent confirmed **allergic IgE-mediated asthma** (e.g. positive skin test to a recognised respiratory allergen)
- Administration: given subcutaneously every 2 or 4 weeks.
- Side effects: injection site pain, swelling, erythema, pruritus, and headaches

Non-pharmacological management

- · Stop smoking.
- Weight-loss interventions
- Breathing exercise programs (including physiotherapist-taught methods) can be offered to
 people with asthma as an adjuvant to pharmacological treatment to improve quality of life
 and reduce symptoms
 - ⇒ Diaphragmatic breathing, (as opposed to thoracic breathing which is practised by many asthmatics): reduce symptoms
 - ➡ Buteyko technique: a breathing technique which can 'improve asthma symptoms, quality of life and reduce bronchodilator (blue reliever inhaler) requirement

Omalizumab

- anti-lgE monoclonal antibody
- used for resistant asthma with evidence of raised IgE and allergic symptoms.

Mepolizumab

- anti-IL5 monoclonal antibody
- used for <u>resistant asthma</u> with <u>raised eosinophils</u>

B-blockers, <u>including eye drops</u>, should be avoided in patients with asthma. They are not however absolutely contraindicated.

Acute severe asthma

Classification of acute severe asthma

- Patients with acute severe asthma are stratified into moderate, severe or lifethreatening.
- Note that a patient having any one of the life-threatening features should be treated as having a life-threatening attack.

Moderate	Severe	Life-threatening
 PEFR 50-75% best or predicted Speech normal RR < 25 / min Pulse < 110 bpm 	 PEFR 33 - 50% best or predicted Can't complete sentences in one breath RR > 25/min Pulse > 110 bpm 	 PEFR < 33% best or predicted Oxygen sats < 92% PaO₂ < 8 kPa Normal PaCO₂ (4.6-6.0 kPa) Silent chest, cyanosis or feeble (Poor) respiratory effort Bradycardia, dysrhythmia or hypotension Exhaustion, confusion or coma

Management of acute severe asthma

Magnesium sulphate - monitor reflexes + respiratory rate

- β2-agonists should be administered as soon as possible, preferably nebulised driven with high flow oxygen.
 - ⇒ salbutamol administration can rapidly worsen the V/Q mismatch which is the cause of hypoxia in asthma. They can therefore cause reduction in arterial oxygen tension unless supplemental oxygen is given
- **Nebulised ipratropium bromide**. It's addition produces significantly greater bronchodilation than a β2-agonist alone.
- Oxygen: Targeted oxygen in asthma → SpO2 level of 94–98%.
- Steroids:
 - steroids reduce mortality, relapses, subsequent hospital admission and requirement for β2-agonists1.
 - ⇒ This should be continued for five days, and can then be stopped abruptly.
- Magnesium sulphate recommended as next step for patients who are not responding (e.g. 1.2 - 2g IV over 20 mins).
 - ⇒ Mechanism: low magnesium levels in bronchial smooth muscle favour bronchoconstriction.
 - ⇒ reduce rates of admission to intensive therapy units
- Intensive care is indicated for patients with severe acute or life threatening asthma who
 are failing to respond to therapy.
 - ⇒ Strongest indicator of a need for intubation and ventilation →PH 7.31

Asthmatic patient with + PaCO2 at the upper limit of normal. What would be the most appropriate next step?

- ⇒ A normal or elevated pCO2 in an asthmatic indicates impending respiratory failure
- ⇒ review by an anaesthetist/intensivist is the next immediate step.
- Hypercapnia and signs of fatigue are indications for immediate intubation and ventilation.

Management of Asthma in pregnancy

- In general, the medicines used for asthma are safe during pregnancy.
- The British Thoracic Society (BTS) guidelines make it clear that short-acting /long-acting beta 2-agonists, inhaled and oral corticosteroids should all be used as normal during pregnancy.
- The BNF advises that 'inhaled drugs, theophylline and prednisolone can be taken as normal during pregnancy and breast-feeding'.

Chronic Obstructive Pulmonary Disease(COPD)

Definition: airflow obstruction that is not fully reversible.

Epidemiology:

- worldwide prevalence of 10%
- · COPD is the third leading cause of death worldwide

Subtypes of COPD

- Chronic bronchitis: defined as chronic cough and sputum production for at least three
 months of two consecutive years in the absence of other disease which could explain
 these symptoms.
- 2. Emphysema

Pathophysiology

- Inflammatory changes → ciliary dysfunction and <u>increased goblet cell size and number</u>,
 → excessive mucus secretion.
- Increased airway resistance is the physiological definition of COPD.
- Decreased elastic recoil, fibrotic changes in lung parenchyma, and luminal obstruction of airways by secretions all contribute to increased airways resistance.
- Progressive hypoxia → vascular smooth muscle thickening → pulmonary hypertension
- Which mechanism is most likely responsible for the increased mean arterial pulmonary pressure in COPD?
 - Hypoxic induced pulmonary vasoconstriction

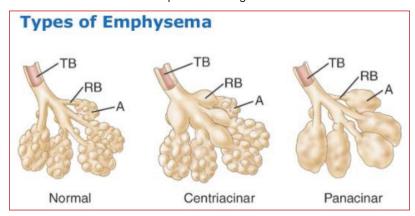
Causes

- Smoking
- Alpha-1 antitrypsin deficiency
- Using open fires at homes for cooking or heating (patients from the developing world present with a COPD-like history without smoking history)
- Occupational exposures, such as harmful dust and chemicals
 - ⇒ cadmium (used in smelting) (recognised cause of emphysema specifically)
 - ⇒ coal, cotton, cement, grain

Emphysema

- Definition
 - ⇒ emphysema is a term that refers to the actual damage to the air sacs in the lung, called the alveoli. In other words, emphysema is a pathological term.
- Pathophysiology
 - destruction of alveolar air sacs due to an imbalance between protease and antiprotease action.
 - ⇒ loss of elastic recoil, which drives airflow limitation.
- Types
 - ⇒ Panlobular (panacinar) pulmonary emphysema
 - Rare
 - Associated with α1-antitrypsin deficiency
 - Characterized by destruction of the entire acinus
 - Usually affects the lower lobe
 - ⇒ Centrilobular or proximal acinar pulmonary emphysema
 - Common
 - Classically seen in smokers

- Characterized by destruction of the respiratory bronchiole (central portion of the acinus)
- Usually affects the upper lobe
- most severe at the apex of the lung.



Types of emphysema

Туре	Centriacinar (centrilobular)	Panacinar
Prevalence	the most common type	Less common
destruction	focal destruction mainly localized to the proximal respiratory bronchioles	destroys the entire alveolus uniformly
Location	upper lung zones.	lower half of the lungs.
causes	smoking & dust	alpha 1-antitrypsin (AAT) deficiency

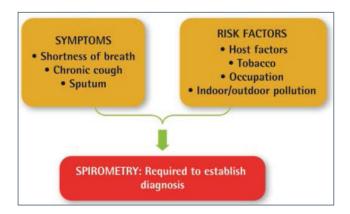
MRCPUK-part-1-septemper-2017: What is the most important factor in airflow limitation in severe emphysema?

⇒ Loss of elastic recoil

Features and complications

- Chronic cough, SOB and recurrent infection
- extensor plantar response is common in (COPD) due to carbon dioxide retention, which results in carbon dioxide narcosis.
- Cor pulmonale
 - ⇒ features include peripheral oedema, raised jugular venous pressure, systolic parasternal heave, loud P2
 - ⇒ use a loop diuretic for oedema, consider long-term oxygen therapy
 - ⇒ ACE-inhibitors, calcium channel blockers and alpha blockers are not recommended by NICE
- Polycythaemia

COPD - Investigation and diagnosis



Who should be suspected of COPD?

NICE recommend considering a diagnosis of COPD in patients over 35 years of age
who are smokers or ex-smokers and have symptoms such as exertional
breathlessness, chronic cough or regular sputum production.

Investigations recommended in patients with suspected COPD:

- spirometry
 - Post-bronchodilator spirometry to demonstrate airflow obstruction: FEV1/FVC ratio less than 70%
- Chest x-ray
 - ⇒ hyperinflation, bullae, flat hemidiaphragm.
 - ⇒ Also, important to exclude lung cancer
- Full blood count: exclude secondary polycythaemia
- Body mass index (BMI) calculation
- methacholine challenge
 - ⇒ useful in differentiating between asthma and chronic obstructive pulmonary disease (COPD).
 - ⇒ methacholine utilizes the M3 receptor for bronchoconstriction.
- ABG
 - ⇒ In long standing COPD the bicarbonate is likely to be normal, or raised if the patient has chronic hypercapnia. (a low pH, low pO₂, high pCO₂ and a high HCO₃)

Severity of COPD: categorised by using the FEV1:

Post-bronchodilator FEV1/FVC	FEV1 (of predicted)	Severity
< 0.7	> 80%	Stage 1 - Mild
< 0.7	50-79%	Stage 2 - Moderate
< 0.7	30-49%	Stage 3 - Severe
< 0.7	< 30%	Stage 4 - Very severe

COPD: causes of acute exacerbations

- Infective exacerbation of COPD is the most common cause of haemoptysis in UK patients
- · bacterial organisms
 - ⇒ Haemophilus influenzae (most common cause of COPD exacerbation)
 - ⇒ Streptococcus pneumoniae
 - ⇒ Moraxella catarrhalis
- Respiratory viruses: account for around 30% of exacerbations, with the human rhinovirus being the most important pathogen.

COPD: management of acute exacerbations

- Bronchodilator
- Steroids: prednisolone 30 mg daily for 7-14 days. Prolonged courses offer no additional benefit
- Antibiotics: It is common practice for all patients with an exacerbation of COPD to receive
 antibiotics. NICE do not support this approach. They recommend giving oral antibiotics 'if
 sputum is purulent or there are clinical signs of pneumonia'
- Oxygen management of COPD patients
 - ⇒ If the patient have an individual target range: Oxygen should be given to maintain SaO2 within the patient's individual target range, if available
 - ⇒ If the individual target is not known:
 - prior to availability of blood gases (pCO2 is unknown):
 - saturations should be maintained at 88-92% to avoid risk of hypercapnia
 - after availability of blood gases (pCO2 is normal): adjust target range to 94-98%
- Non-invasive ventilation
- Respiratory stimulants (e.g. Doxapram)
 - □ In COPD exacerbations, respiratory stimulants (e.g. Doxapram) should only be used when Non-invasive ventilation is either unavailable or considered inappropriate

COPD: stable management

COPD - reason for using inhaled corticosteroids - reduced exacerbations

COPD - still breathless despite using inhalers as required?

FEV1 > 50%: LABA or LAMA

FEV1 < 50%: LABA + ICS or LAMA

COPD - LTOT if 2 measurements of pO2 < 7.3 kPa

General management

- · smoking cessation advice
- · annual influenza vaccination
- · one-off pneumococcal vaccination

Pharmacological therapy

- first-line:
 - ⇒ short-acting beta2-agonist (SABA) or short-acting muscarinic antagonist (SAMA)
- second-line:
 - ⇒ for patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by the FEV1
 - FEV1 > 50%
 - long-acting beta2-agonist (LABA), for example salmeterol, or:
 - long-acting muscarinic antagonist (LAMA), for example tiotropium
 - FEV1 < 50%
 - ❖ LABA + inhaled corticosteroid (ICS) in a combination inhaler, or:
 - LAMA
- Third-line:
 - ⇒ For patients with persistent exacerbations or breathlessness
 - if taking a LABA then switch to a LABA + ICS combination inhaler
 - otherwise give a LAMA and a LABA + ICS combination inhaler

Factors to consider when initiating inhaled corticosteroids (ICS) for COPD (GOLD guidelines January 2021)				
Strong support	Consider use	Against use		
 History of hospitalization for exacerbation of COPD ≥ 2 moderate exacerbation of COPD per year Blood eosinophils > 300 cells/ml History of, or concomitant asthma 	 1 moderate exacerbation of COPD per year Blood eosinophils 100 – 300 cells/ml 	 Repeated pneumonia events Blood eosinophils < 100 cells/ml History of mycobacterial infection 		

Other pharmacological therapies

- Oral theophylline
 - ⇒ NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot used inhaled therapy
 - the dose should be reduced if macrolide or fluoroquinolone antibiotics are coprescribed
- Mucolytics: should be 'considered' in patients with a chronic productive cough and continued if symptoms improve
- LTOT : should be offered to:
 - ⇒ patients with a pO2 of < 7.3 kPa or
 - ⇒ patients with a pO2 of 7.3 8 kPa and one of the following:

- secondary polycythaemia
- nocturnal hypoxaemia
- peripheral oedema
- pulmonary hypertension

Roflumilast

- □ Indication:
 - recommended by NICE for patients who have suffered two or more exacerbations in a year, despite triple inhaled therapy, where FEV1 is less than 50% of predicted.
- ⇒ Mode of action:
 - selective long-acting <u>phosphodiesterase-4 inhibitor.</u>
 - It is orally administered.

Management of side effect of steroid inhaler (Oro-pharyngeal and oesophageal candidiasis)

- the patient should be taught adequate inhaler technique. Advise him to rinse his mouth each time he uses his inhaler and use a spacer device and review him in a month.
- Resistant symptoms can be managed with oral nystatin or a course of fluconazole.

Pulmonary rehabilitation

- Definition: a programme of aerobic lower-extremity training combined with education.
- Indication: Patients with very limited exercise tolerances
- Effects
 - ⇒ It leads to <u>improvements in exercise capacity</u> (walking distance should improve after the rehabilitation programme)
 - ⇒ The improvement in walking distance would not be a long-lasting improvement
 - Decline in exercise tolerance and health status tends to occur 6–12 months after the completion of a course.
 - The effect of sustained improvement with ongoing rehabilitation has yet to be evaluated.
 - ⇒ does not improve lung function.
 - does not decrease hospital admissions because of chest problems, but their hospital stays are likely to be shorter.

Lung volume reduction surgery

- Is a palliative treatment which can be used in advanced COPD to remove the least functional part of the lungs.
- there are 3 groups of patients that tend to benefit:
 - Group 1: Upper lobe emphysema and low exercise capacity.
 - These patients show <u>improvement in both functional outcomes and</u> <u>survival</u> after lung volume reduction surgery compared to medical therapy.
 - Group 2: upper lobe emphysema and high exercise capacity.
 - These patients have <u>improved functional outcomes but no difference in</u> survival compared to medical therapy.
 - Group 3: non-upper lobe emphysema and low exercise capacity.
 - These patients have <u>improved survival after surgery but there is no</u> difference in survival compared to medical therapy.
- patients with emphysema that are unlikely to do well from lung volume reduction surgery and have a high risk of death includes:
 - 1. non-upper lobe emphysema and high exercise capacity.
 - extremely poor pulmonary function (forced expiratory volume in 1 second (FEV1)
 20% or less than predicted) and either homogenous distribution of emphysema on

computed tomography scan or extremely poor carbon monoxide diffusing capacity (20% or less than predicted).

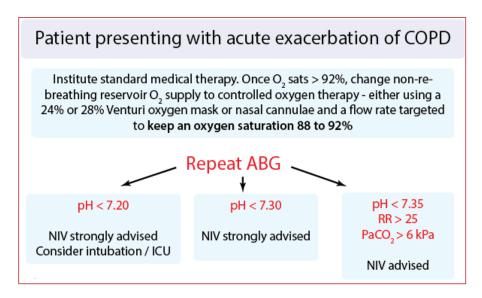
Indications:

- ⇒ CO₂ retention: The upper cut off for referral for lung reduction surgery for pCO₂ is 7.3
- ⇒ Severe limitation of exercise capacity despite maximal therapy
- ⇒ predominant upper lobe emphysema, and persistent symptoms despite a period of pulmonary rehabilitation.
- selection criteria: used when assessing suitability for treatment:
 - ⇒ Age <75 years
 </p>
 - ⇒ Emphysema by clinical evaluation
 - ⇒ Ex-smoker of more than 4 months
 - ⇒ Clinically stable on no more than 20mg prednisolone daily
 - ⇒ Significant functional limitation after 6-12 weeks of pulmonary rehabilitation on optimal medical therapy
 - ⇒ Demonstrated compliance with medical regimen
 - ⇒ FEV-1 >20% predicted
 - ⇒ Post-bronchodilator FEV-1 >45% predicted and >15% if >70 years
 - ⇒ Hyperinflation demonstrated by TLC >100% predicted and RV >150% predicted
 - ⇒ Carbon monoxide lung transfer factor greater than 20% predicted
 - ⇒ Post rehabilitation 6-minute walk distance >140 m
 - ⇒ Low post rehabilitation exercise capacity
 - ⇒ HRCT demonstrating bilateral severe emphysema, ideally with upper-lobe predominance

Symptomatic relief of breathlessness in end-stage COPD (DNR cases)

 opioid or benzodiazepine medications for symptomatic relief of breathlessness is appropriate.

Non-invasive ventilation (NIV)



Indications of NIV

- COPD with respiratory acidosis (pH 7.25-7.35) who have not improved despite immediate maximum standard medical treatment on controlled oxygen for no more than one hour.
 - ⇒ patients with a pH in the range of 7.25-7.35 achieve the most benefit.
 - ⇒ If the pH is < 7.25 then invasive ventilation should be considered if appropriate.
- Type II respiratory failure secondary to chest wall deformity, neuromuscular disease or Obstructive sleep apnoea
- 3. Cardiogenic pulmonary oedema
- 4. Weaning from tracheal intubation

Advantage of NIV

- · reduce intubation rates
- · lower hospital mortality rates and
- lead to shorter hospital stays

Recommended initial settings for bi-level pressure support in COPD

- Inspiratory Positive Airway Pressure (IPAP): RCP advocate 10 cm H20 whilst BTS suggest 12-15 cm H2O.
- Expiratory Positive Airway Pressure (EPAP): 4-5 cm H2O
- back up rate: 15 breaths/min
- back up inspiration: expiration ratio: 1:3

Monitoring and setting adjustment

- ABGs should be repeated <u>after 1 hour</u> of NIV therapy, and <u>1 hour after subsequent change</u> in settings or <u>4 hours in stable patients</u>.
 - ⇒ If gas exchange is not significantly improved:
 - the IPAP can be gradually increased at a rate of approximately <u>5 cms (2-5cm)</u>
 H2O every 10 minutes with a <u>usual target of 20cm H2O</u> or until a response has been achieved or patient tolerability has been reached.
 - Increases in EPAP are not recommended without specialist advice.

- If the patient struggle to tolerate the NIV mask, what is the most appropriate method to help him settle him?
 - ⇒ haloperidol or morphine
 - Decreasing the IPAP or stopping NIV would be more comfortable but would be inappropriate as treatment is then likely to fail with greater hypoxia and acidosis.
 - Diazepam is contraindicated
 - Increasing EPAP without increasing IPAP would reduce the amount of ventilatory support and would be inappropriate.

Complication of NIV

- ventilation associated pneumothorax is (most important complication of NIV → present acutely)
- Ventilator associated pneumonia → present in patients who have been ventilated for long period of time and would not present so acutely).

Contraindications to NIV

- Absolute contraindications:
 - ⇒ inability to fit the NIV mask appropriately,
 - ⇒ cardiopulmonary arrest, and need for urgent intubation
- · Relative contraindications
 - haemodynamically unstable requiring inotropes/pressors (unless in a critical care unit)
 - ⇒ confusion/agitation

NIV modes

- Continuous positive airway pressure (CPAP)
 - As this mode only provides a continuous pressure, CPAP is a spontaneous mode of ventilation that requires patient initiation and respiratory muscle effort. Therefore, no respiratory rate or minute ventilation is targeted or guaranteed.
 - ⇒ The clinical benefit of CPAP is most evident in hypoxemic respiratory failure as the positive airway pressure predominately augments oxygenation with the goal of recruiting alveoli, increasing functional residual capacity, and decreasing shunting.
 - ⇒ Inspiration during IPPV → ↑↑ intrathoracic pressure → ↑↑ right atrial pressure → ↓↓ venous return →↓↓ cardiac output
- Bilevel positive airway pressure (BiPAP)
 - ⇒ in contrast to CPAP, provides both an expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP).
 - ⇒ BiPAP has utility in both hypoxemic and hypercarbic respiratory failure.

Minute ventilation

- Minute ventilation is equal to tidal volume (volume of air moved in normal breathing) multiplied by the respiratory rate.
- In metabolic alkalosis, one could increase CO₂ content by decreasing the minute ventilation (volume of air moved per minute).
- Reducing either one of these variables(↓tidal volume or ↓ respiratory rate) will
 decrease minute ventilation and lead to increased CO₂ retention.

•

Invasive ventilation

Indications

- · unconscious patient
- if the pH is below 7.25.
 - ⇒ Patients with a pH <7.26 should be managed with a low threshold for intubation.
 - ⇒ give NIV whilst waiting for intensive care.
- in Guillain Barre syndrome with respiratory involvement → the parameter used to assess whether a patient needs ventilator support is an FVC <15-20ml/kg.

Ethics in decision to ventilate

- If the patient had a written advanced directive, properly witnessed, **while he was well**, then it would not be possible to consider intervention if he wished for it not to happen.
- if he has significant hypoxia, he might not be able to give a rational decision with respect to his further treatment.
- if significantly hypoxic patient refused intubation during acute exacerbation →
 Intubate and act on the best interests of the patient, while informing the relatives
- The family should not have the final decision with respect to intubation.

Long-term oxygen therapy (LTOT)

COPD - LTOT if 2 measurements of pO2 < 7.3 kPa

Which patients should be assessed for and offered (LTOT)?

- Assess patients if any of the following:
 - ⇒ Very severe airflow obstruction (FEV1 < 30% predicted).
 - ⇒ cvanosis
 - ⇒ polycythaemia
 - ⇒ peripheral oedema
 - ⇒ raised jugular venous pressure
 - ⇒ oxygen saturations less than or equal to 92% on room air

How to assess patient for LTOT?

- ⇒ Assessment is done by measuring <u>arterial blood gases</u> on <u>2 occasions</u> at least <u>3 weeks</u> <u>apart</u> in patients with <u>stable COPD</u> on optimal management.
- ⇒ Blood gases should be performed in a <u>stable state</u>, which should be at least <u>four weeks</u> after an exacerbation of the disease.

Indications for LTOT in COPD:

- patients with pO2 of < 7.3 kPa
- patients with pO2 of 7.3 8 kPa and one of the following:
 - ⇒ secondary polycythaemia
 - ⇒ nocturnal hypoxaemia
 - ⇒ peripheral oedema
 - ⇒ pulmonary hypertension

Duration of LTOT

Patients who receive LTOT should breathe supplementary oxygen for at least 15 hours a
day including at night time.

Contraindications

• Continued cigarette smoking should be a <u>relative</u> contraindication to long-term oxygen therapy.

In patients with chronic hypoxaemia, LTOT should be prescribed after assessment, when the PaO_2 is consistently at or below 7.3 kPa (55 mm Hg) when breathing air during a period of clinical stability. Clinical stability is defined as the absence of exacerbation of chronic lung disease for the previous five weeks.

The level of PaCO₂ (which may be normal or elevated) does not influence the need for LTOT prescription.

The only treatment that improves the long-term prognosis in patients with (COPD) is LTOT, given for at least 15 hours per day.

Patients who develop a respiratory acidosis and/or a rise in PaCO2 of >1 kPa (7.5 mmHg) during an LTOT assessment on two repeated occasions, while apparently clinically stable, should only have domiciliary oxygen ordered in conjunction with nocturnal ventilatory support.

How will you manage this patient?

- ⇒ LTOT with nocturnal BiPAP
 - BiPAP is the modality of choice for treating CO2 retention.

Prognosis of COPD

- Once respiratory failure criteria have been met, the 5-year survival rate is only around 25%.
- Prognostic indicators in COPD
 - ⇒ The strongest predictors of survival in patients with (COPD) are FEV1
- Factors, which may improve survival in patients with stable COPD
 - smoking cessation. the single most important intervention in patients who are still smoking
 - ⇒ long term oxygen therapy in patients who fit criteria
 - ⇒ lung volume reduction surgery in selected patients

Pulmonary embolism (PE)

Pathophysiology 4 1 2 1

PE → ↓ lung blood flow → ventilation- perfusion mismatches (Decreased perfusion + normal ventilation) → ↑ physiologic dead space.

Risk factors

The Virchow triad pathophysiological components of thrombus formation:

- 1. **Hypercoagulability**: thrombophilia (e.g., factor V Leiden mutation), use of oral contraceptives, pregnancy.
- 2. **Endothelial damage**: inflammatory or traumatic → activation of clotting factors through contact with exposed subendothelial collagen.
- 3. **Stasis** (e.g. varicosis, immobilization)

Major risk factors	Minor risk factors
 lower limb problems including a fracture or varicose veins postoperative intensive care hospitalisation abdominal/pelvic or advanced malignancy previous VTE, and pregnancy. 	 occult malignancy long distance travel hypertension congestive cardiac failure thrombotic disorder use of the oral contraceptive pill

Features

Sudden shortness of breath, pleuritic chest pain with haemoptysis and tachypnoea are the commonest features. (triad of pleuritic chest pain, dyspnoea and haemoptysis)

- Tachypnea (respiratory rate >16/min) 96% (Sudden shortness of breath)
- Pleuritic chest pain (worse on deep breathing)
- haemoptysis
- Tachycardia (heart rate >100/min) 44%
- Fever (temperature >37.8 C) 43%.

Diagnosis

- If a patient presents with signs or symptoms of pulmonary embolism (PE)
 - ⇒ performed chest x-ray to exclude other pathology
 - ⇒ estimate the clinical probability of PE by two-level PE Wells score

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

Clinical probability simplified scores			
PE likely More than 4 points			
PE unlikely	4 points or less		

• PE likely (> 4 points):

- ⇒ arrange an immediate computed tomography pulmonary angiogram (CTPA).
 - If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.
 - If the patient has an allergy to contrast media or renal impairment a Ventilation-perfusion (V/Q) scan should be used instead of a CTPA.

• PE unlikely (≤ 4 points):

- ⇒ arranged a D-dimer test:
 - If this is positive arrange an immediate (CTPA).
 - If there is a delay in getting the CTPA then give low-molecular weight heparin until the scan is performed.

It is interesting to note that the Well's criteria for diagnosing a PE use tachycardia rather than tachypnoea.

Pulmonary embolism - normal CXR

Investigations

Pulmonary embolism - CTPA is first-line investigation

Chest x-ray

- ⇒ Should be performed in all patients with symptoms or signs suggestive of PE
- ⇒ to exclude other pathology
- ⇒ usually normal in PE
- Computed tomographic pulmonary angiography (CTPA)
 - ⇒ the first-line diagnostic test
 - ⇒ If the CTPA is negative then patients do not need further investigations or treatment for PE
 - ⇒ Disadvantages of CTPA:
 - Contrast induced nephropathy
 - Low sensitivity for detecting pulmonary emboli in sub-segmental pulmonary arteries

Ventilation-perfusion (V/Q) scans

- ⇒ Indication? → If CTPA is contra-indicated
 - renal impairment (as the contrast media used during CTPAs is nephrotoxic).
 - allergy to contrast media
- ⇒ Sensitivity = 98%; specificity = 40% → high negative predictive value, i.e. if normal virtually excludes PE
- \Rightarrow In pregnancy \rightarrow Radiation to the fetus is small.

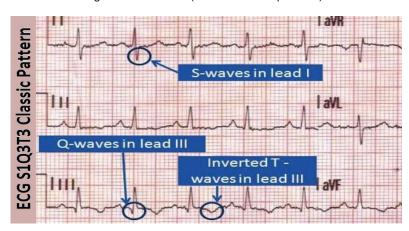
D-dimers

- ⇒ Should be performed ONLY when the probability of PE is low, so the normal value would be taken as reassuring and further investigation would not be pursued.
- ⇒ High sensitivity (95-98%), but poor specificity

- A negative d-dimer is useful for excluding PE in patients who are clinically thought to be at low risk, but a 'positive' result does not establish the diagnosis.
- The negative predictive value is greater than the positive predictive value
- ⇒ D-dimers can be positive in:
 - hospitalised patients
 - obstetric patients
 - patients with peripheral vascular disease, cancer and inflammatory conditions
 - increasing age
- ⇒ D-Dimer measurements should not be performed if:
 - an alternative diagnosis is likely.
 - the clinical probability is high or
 - there is a probable massive PE.

ECG

- ⇒ sinus tachycardia
 - the most common abnormality; seen in 44% of patients.
- ⇒ the classic ECG changes → S1Q3T3 (seen in no more than 20% of patients)
 - large S wave in lead I
 - large Q wave in lead III
 - inverted T wave in lead III.
- ⇒ Right bundle branch block
 - seen in 18% of patients.
 - associated with increased mortality;
- ⇒ Right axis deviation (seen in 16% of patients).



 Elevated cardiac troponin levels also occur in patients with pulmonary embolism because of right ventricular dilation and myocardial injury

Management

Start low molecular weight heparin and request CT pulmonary angiography if the symptoms and findings clearly point towards pulmonary embolism (PE).

Fluid resuscitation is the most appropriate immediate measure before further investigations confirm the presence of a pulmonary embolism (PE).

Massive PE + hypotension - thrombolyse

Anticoagulant

- ⇒ First-line: apixaban or rivaroxaban
- ⇒ Second-line: (if apixaban or rivaroxaban are not suitable)
 - LMWH for at least 5 days followed by dabigatran or edoxaban OR
 - LMWH concurrently with a vitamin K antagonist (warfarin) for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by a VKA on its own.
- ⇒ For patients with positive antiphospholipid syndrome → the 1st line is LMWH concurrently with a VKA.
- ⇒ Duration of anticoagulant:
 - For most patients →3 months
 - with active cancer →3 to 6 months.
 - For unprovoked DVT or PE→ Consider continuing anticoagulation beyond 3 months (6 months for people with active cancer) → use the HAS-BLED score for major bleeding risk → stop anticoagulation if the HAS-BLED score is 4 or more and cannot be modified.
- ⇒ Heparin
 - When should be started?
 - For patients with a high or intermediate probability of a non-massive PE → low molecular weight heparin should be given before imaging
 - $\ \ \, \ \ \,$ For patient with low probability of non-massive PE \rightarrow immediately after diagnosis.
 - Which type?
 - ❖ For non-massive PE →Low molecular weight heparin (LMWH) or fondaparinux.
 - For patients with severe renal impairment ([eGFR] <30 ml/min/1.73 m²) offer either:</p>
 - unfractionated heparin (UFH) with dose adjustments based on the APTT **or**
 - LMWH with dose adjustments based on an anti-Xa assay.
 - For patients with an increased risk of bleeding consider UFH.
 - ❖ For massive PE where thrombolysis is being considered, → unfractionated heparin should be used.
 - Benefit of heparin?
 - Heparin reduces risk of further embolism (anticoagulant) and reduces pulmonary vasoconstriction.
- Thrombolysis
 - ⇒ Indication?
- Massive PE where there is haemodynamic instability demonstrated by hypotension, right ventricular strain on an ECG or signs of right heart failure.
- Cardiac arrest situation for suspected PEs. However, it can take 90 minutes to be effective
 and therefore must only be used if it is appropriate to continue CPR for this duration.
- ❖ Cardiac arrest for suspected PEs → Intravenous thrombolysis followed by CPR for 90 minutes
- ⇒ Which drug?

- Alteplase 100 mg over 1.5 hours peripherally.
- Thrombolysis administered through a peripheral vein is as effective as through a pulmonary artery catheter
- Percutaneous insertion of Inferior vena cava (IVC) filter
- ⇒ Indication?
- If anticoagulation is a contraindicated (eg PE following a recent haemorrhagic stroke)
- if anticoagulation alone fails
- ⇒ Benefit of IVC filter?
- may be as effective as anticoagulation.

Recurrent pulmonary emboli

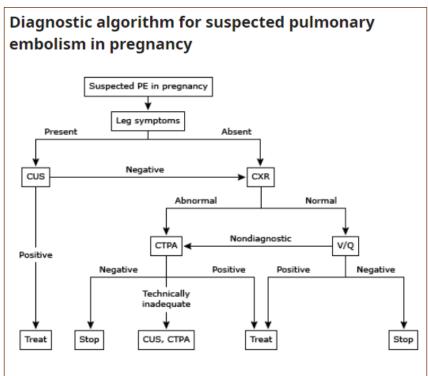
- Recurrent pulmonary emboli should always be considered in cases of progressive shortness of breath with no obvious cause.
- Predisposing factors for recurrent pulmonary embolism include:
 - ⇒ Antithrombin III deficiency
 - ⇒ Protein C deficiency
 - ⇒ Factor V Leiden mutation
- **Possible clues** include pulmonary hypertension, right ventricular enlargement, hypoxia with a low PaCO2 and a low transfer factor.
- Widening of the alveolar-arterial (A-a) gradient on exercise is likely to be found.
- Mismatched defects are classic features of pulmonary embolus.
- Consider inferior vena caval filters for patients with recurrent proximal DVT or PE despite adequate anticoagulation treatment only after considering alternative treatments such as:
 - ⇒ increasing target INR to 3–4 for long- term high-intensity oral anticoagulant therapy **or**
 - ⇒ switching treatment to LMWH.

Pulmonary embolism in pregnancy: diagnosis and management

Diagnosis

- Chest x-ray and ECG to look for an alternative diagnosis such as pneumonia and pneumothorax.
- If the chest x-ray is normal:
 - In women with suspected PE who also have symptoms and signs of DVT →
 consider a compression duplex doppler of both legs to exclude a DVT.
 - this may provide indirect evidence of a pulmonary embolism and negate the need for further radiation exposure
 - If this is positive, the patient is treated with full dose low molecular weight heparin (LMWH) (warfarin is of course teratogenic).
 - ⇒ In women with suspected PE without symptoms and signs of DVT → ventilation/perfusion (V/Q) lung scan or a computerised tomography pulmonary angiogram (CTPA) should be performed.
- When the chest X-ray is abnormal and there is a clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan. [New 2015]

- CTPA vs V/Q scan
 - ⇒ CTPA → ↑risk of maternal breast cancer
 - ⇒ V/Q scanning → ↑risk of childhood cancer
- D-dimer is of limited use as it often raised in pregnancy.



PE: pulmonary embolism; CUS: compression ultrasound; CXR: chest radiography; CTPA: computed-tomographic pulmonary angiography; V/Q: ventilation-perfusion.

Treatment of PE in pregnancy

- In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing
- 1st line: **low-molecular-weight heparin (LMWH)** should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total.
- 2nd line: In pregnant women who are unable to tolerate heparin (LMWH or unfractionated heparin) or danaparoid and who require continuing anticoagulant therapy
 → use the newer anticoagulants (fondaparinux, argatroban or r-hirudin)
- Unfractionated heparin (UFH)
 - ⇒ UFH is the preferred, initial treatment in massive PE with cardiovascular compromise.

- ⇒ platelet count monitoring should be performed every 2–3 days from days 4 to 14 or until heparin is stopped.
- Warfarin should not be used for antenatal VTE treatment.
- Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of postpartum haemorrhage.

Post-thrombotic syndrome (PTS)

- Develop in nearly 50% of all patients who experience a DVT.
- Features: chronic leg pain, swelling, redness, and ulcers.
- Prevention: prolonged use of LMWH (more than 12 weeks).

References

Royal College of Obstetricians and Gynaecologists guidelines (Update August 2018)

Fat embolism

The classic triad of presentation is:

- Eosinophilia
- · Acute renal failure and
- Livedo reticularis.

Definition

Entry of fat particles usually from bone marrow, in the pulmonary circulation.

Causes

- Traumatic (95%):
 - most commonly associated with long bone (especially femur) and pelvic fractures.
 - ⇒ typically manifests 24 to 72 hours after the initial insult.
- Non-traumatic (Rare): Sickle cell crisis, pancreatitis, osteomyelitis.

Features

- The classic **triad of hypoxemia**, **neurologic abnormalities** (eg, confusion, altered consciousness, seizure), and a **petechial rash**.
- Less common: anemia, thrombocytopenia, fever, lipiduria, and coagulation abnormalities;
- · Rare: myocardial depression and shock

Diagnosis

- · Presence of clinical triad
- Exclusion of other possible causes
 - ⇒ embolization syndromes (thrombus, amniotic fluid, tumor, foreign body, air),
 - ⇒ acute alveolar filling diseases (eg. heart failure, pneumonia, and ARDS) and
 - ⇒ cutaneous vasculitic disorders (eg, systemic lupus erythematosus).

Treatment

- Supportive
 - ⇒ Intravenous (iv) fluids to maintain high right ventricular filling pressures.
 - ⇒ High flow oxygen
 - ⇒ Diuretic treatment would be strongly contraindicated in this case. This is because right ventricular output is dependent on elevated filling pressures. Reducing the preload is therefore not a good idea.
- Steroids are reserved for severe or refractory cases.
- Most patients fully recover spontaneously.

The diagnosis of cholesterol embolism should be considered in any patient with atherosclerotic disease presenting with deteriorating renal function, multisystem disease or distal ischaemia developing after an invasive arterial procedure.

Community-acquired pneumonia (CAP)

Definition

Pneumonia acquired outside hospital or healthcare facilities.

Streptococcus pneumoniae is associated with cold sores

Preceding influenza predisposes to Staphylococcus aureus pneumonia

Both Klebsiella and Staphylococcus are associated with empyema formation and cavitating lung lesions.

Causes

- Streptococcus pneumoniae
 - ⇒ the most common cause of CAP & single lobar pneumonia (80%)
 - ⇒ Streptococcus pneumoniae commonly causes reactivation of the herpes simplex virus resulting in 'cold sores' → herpes labialis
 - S. pneumoniae is the most important cause of fulminant sepsis in patients with hyposplenism.
- Haemophilus influenzae
 - ⇒ more likely to be associated with exacerbations of COPD
- Staphylococcus aureus
 - ⇒ commonly after the 'flu .
 - ⇒ It's an organism often found on the skin. It is therefore commonly associated with systemic infections in intravenous drug users ,this is may hinted in questions by the presence of track marks.
 - ⇒ It also causes a **bibasal pneumonia** as opposed to *Streptococcus* pneumoniae that is the most common cause of a single lobar pneumonia.

- ⇒ seen most frequently in the elderly and in intravenous drug users or patients with underlying disease.
- ⇒ It can result in a cavitating pneumonia.
- Carries a high mortality, and therefore if suspected treatment should initially be for a severe CAP.
- ⇒ Capable of production of Panton-Valentine-Leucocidin toxin , associated with severe illness and high mortality.
- ⇒ Pneumothorax, pleural effusion and empyema are common in staphylococcal pneumonia.
- ⇒ the BNF advises the co-prescription of flucloxacillin.

 \Rightarrow

Atypical pneumonias due to:

- ⇒ Mycoplasma pneumoniae ,
- ⇒ Legionella pneumophila .
- ⇒ Coxiella burnetii (Q fever) → relation to animal sources (usually sheep).
- ⇒ Chlamydophila psittaci → bird contact (eg, poultry or duck workers)
- ⇒ Chlamydophila pneumophila

Viruses

Some studies have found that influenza virus is the most common cause of CAP in adults.

• Klebsiella pneumoniae

- Classically occurs in alcoholics (Friedlander's pneumonia) and immunosuppressed individuals
- ⇒ can cause cavitating pneumonia
- ⇒ usually affects the upper lobes
- ⇒ Chest x-ray features may include abscess formation in the middle/upper lobes and empyema.
- ⇒ The mortality approaches 30-50%.

Features

- Respiratory symptoms (e.g. cough, often with increasing sputum production, expectoration, dyspnoea, pleuritic pain, and haemoptysis)
- Signs of infection (fever or chills and leukocytosis)
- Non-specific symptoms such as myalgia and arthralgia.
- Specific features of some causes of pneumonia:
 - ⇒ Legionellosis can present with headache, confusion, digestive manifestations such as diarrhoea, and clinical manifestations of hyponatraemia.
 - ⇒ Mycoplasma pneumoniae may present with extrapulmonary manifestations such as myringitis, encephalitis, uveitis, iritis, and myocarditis
- Elderly patients may present atypically, often afebrile, with confusion and worsening of underlying diseases.

Investigations

Chest x-ray

Organism	Characteristic chest x-ray
Streptococcus pneumoniae	lobar consolidation
Legionella	bibasal consolidation
Staphylococcus aureus	bilateral cavitating bronchopneumonia,

- · Leukocytosis.
- Biomarkers (useful for predicting inadequate host response.)
 - ⇒ C-reactive protein (CRP) >100 mg/L makes pneumonia likely.
 - ⇒ Procalcitonin (PCT)
 - Elevated PCT are correlated with bacterial pneumonia whereas lower values are correlated with viral and atypical pneumonia.
 - PCT is especially elevated in cases of pneumococcal pneumonia.

Management

Mild community acquired pneumonia (CURB 0-1) should be treated with oral penicillin therapy alone assuming no allergies and no other complicating factors

- Assessed the severity of pneumonia using (CURB-65 score)
 - ⇒ CURB-65 score criteria
 - 1. Confusion (abbreviated mental test score ≤ 8/10)
 - 2. Urea > 7 mmol/L
 - 3. Respiratory rate ≥ 30 / min
 - 4. **BP**: systolic ≤ 90 or diastolic ≤ 60 mmHg
 - 5. age ≥ **65** years
 - \Rightarrow CURB-65 score of 0 1 can be managed in the community.
 - ⇒ CURB-65 score of 2 or more should be managed in hospital as this represents a severe community acquired pneumonia.
- Empirical antibiotics
 - A summary table of empirical antibiotics as suggested by the BTS is shown below.

Pneumonia Severity (based on clinical judgement and CURB score)	Treatment Site	First line	Second line
Low Severity (CURB65 = 0-1)	Home	Amoxicillin orally	Doxycycline or clarithromycin orally
Moderate severity (CURB65 = 2)	Hospital	Amoxicillin plus clarithromycin orally (IV if oral administration not possible)	Doxycycline, Levofloxacin or moxifloxacin orally
High Severity (CURB65 = 3-5)	Hospital	Co-amoxiclav plus clarithromycin IV	Benzylpenicillin plus levofloxacin or ciprofloxacin IV OR Cefuroxime plus clarithromycin IV

- BNF advice: add flucloxacillin if staphylococci suspected (e.g. In influenza)
- Pneumonia possibly caused by atypical pathogens → Clarithromycin
- If <u>Staphylococcus aureus</u> is identified, treatment should be altered:

- ⇒ **Non-MRSA** organisms should be treated with flucloxacillin and/or rifampicin; an alternative for penicillin-allergic patients is teicoplanin and rifampicin.
- ⇒ **MRSA** should be treated with vancomycin.

Panton-Valentine Leukocidin-producing Staphylococcus aureus (PVL-SA)

- a rare cause of high severity pneumonia, associated with rapid lung cavitation (necrotising pneumonia) and multiorgan failure.
- empirical antibiotic combination of IV <u>linezolid</u> 600 mg twice daily, IV <u>clindamycin</u>
 1.2 g four times a day and IV rifampicin 600 mg twice daily

Prognostic factors

- Factors associated with a poor prognosis include:
 - ⇒ ↑ CURB-65 score
 - CURB-65 score of 4 → mortality rate at 30 days = 30%.
 - ⇒ Co-morbidity such as renal disease, DM, chronic lung disease, heart failure
 - ⇒ hypoxaemia (pO2 < 8 kPa) independent of FiO2
 - ⇒ White cell count less than 4 ×109/L or greater than 20 ×109/L
 - ⇒ Multi-lobar involvement on CXR.
 - ⇒ Temperature less than 35°C or more than 40°C.
 - ⇒ Thrombocytosis is associated with increased mortality compared to thrombocytopaenia or normal platelet levels.

The risk of mortality increases as the CURB score increases

Score	Risk of death at 30 days	
0 to 1	<5% mortality	
2 to 3	< 10% mortality	
4 to 5	15-30% mortality	

· How quickly their symptoms should resolve?

⇒ NICE recommend that the following information is given to patients with pneumonia in terms of how quickly their symptoms should resolve:

Time	Progress
1 week	Fever should have resolved
	Chest pain and sputum production should have substantially reduced
6 weeks	Cough and breathlessness should have substantially reduced
	Most symptoms should have resolved but fatigue may still be present
6 months	Most people will feel back to normal.

Follow up

- What review policy should be adopted in patients managed in the community?
 - ⇒ Review is recommended after 48 h or earlier if clinically indicated for disease severity assessment

- ⇒ Those who fail to improve after 48 h of treatment should be considered for hospital admission or chest radiography.
- C-reactive protein should be re-measured, and a chest radiograph repeated in patients who are not progressing satisfactorily after 3 days of treatment.
- Chest x ray in six weeks to ensure complete resolution.
 - ⇒ What arrangements should be made for follow-up after hospital discharge?
 - Clinical review should be arranged for all patients at around 6 weeks.
 - radiological changes can take up to 6 weeks to improve.
 - ⇒ This is to exclude any underlying cause especially malignancy.
 - ⇒ those who have persistent shadowing on the lung need referral to a respiratory physician.

Klebsiella Pneumonia

Pneumonia in an alcoholic - Klebsiella

Overview

- Klebsiella is a Gram-negative rod (bacillus) encapsulated, non-motile bacterium that is part of the <u>normal gut flora</u>.
- It can cause many infections in humans including pneumonia (typically following aspiration) and urinary tract infections.
- Most frequently causes infection in hospitalized patients and in those with impaired host defenses, including patients with diabetes mellitus, alcoholism, malignancy, hepatobiliary disease, chronic obstructive pulmonary disease, and renal failure,
- It is an uncommon cause of community-acquired pneumonia. is a common cause of nosocomial pulmonary infections

Pathophysiological mechanism

• Colonization of the oropharynx followed by microaspiration of upper airway secretions in the setting of decreased consciousness (due to heavy alcohol drinking).

Features

- more common in alcoholic and diabetics
- · may occur following aspiration
- 'red-currant jelly' sputum
 - ⇒ One stark difference between Streptococcus pneumonia and Klebsiella pneumonia is the type of sputum produced. The sputum produced by S. pneumoniae is described as "blood-tinged" or "rust-colored," however, the sputum blood-tinged by those infected by K. pneumoniae is described as "currant jelly."
- · Cavitating lesions, often affects upper lobes.
- Typically causes a lobar infiltrate that is in the posterior aspect of the right upper lung.
- Another non-specific sign of K. pneumoniae on a chest radiograph is the bulging
 fissure sign. This is related to the large amount of infection and inflammation that the
 organism can cause.
- commonly causes empyema and less commonly lung abscess

Treatment

- Community-acquired K. pneumoniae pneumonia → third-generation cephalosporins or quinolones
- Extended-spectrum beta-lactamase (ESBL) K. pneumoniae → carbapenem therapy

Prognosis

mortality is 30-50%

History of alcoholism and cavitations are suggestive of Klebsiella as the etiology.

Legionella pneumonia (Legionnaires' disease)

Legionella pneumophilia is best diagnosed by the urinary antigen test

Aetiology

- Legionella bacteria are aerobic, gram-negative rod, intracellular pathogens that are commonly found in water and soil. Human infection is typically acquired through inhalation of aerosols from these substances.
- L. pneumophila serotype 1 is the most common cause of human Legionella infections.

Epidemiology

- Cause 2-5% of community-acquired pneumonia admitted to hospital.
- Incubation period 2-10 days
- More common in males and age of > 50 years.
- Can cause outbreaks in large facilities such as hospitals, hotels, or apartment buildings due to contaminated communal water supplies

Source infections

- It is typically **colonizes hot water tanks** and hence questions may hint at airconditioning systems or foreign holidays.
- Factors that encourage colonisation and multiplication are temperature (20-45 °C) and stagnation.

Transmission

- By inhalation of contaminated water droplets (aerosol)
- Person-to-person transmission is not seen

Features

- Flu-like symptoms (present in > 95% of patients), dry cough
- Gastrointestinal symptoms such as nausea, vomiting, and diarrhea
- Elevated hepatic transaminases
- · Relative bradycardia
- Lymphopaenia
 - ⇒ A marked neutrophil leukocytosis may be associated with concomitant lymphopenia.
- Hyponatraemia
 - ⇒ Secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

The classic features of Legionnaires' disease are:

- Recent foreign travel
- · Relative bradycardia
- prominent headache
- Hyponatraemia

Diagnosis

- Urinary antigen
 - the most useful diagnostic test
 - ⇒ Sensitivity 80%; specificity >99%.
 - ⇒ Rapid test
 - ⇒ Only detects *L. pneumophila* serotype 1, so a negative result does not exclude the diagnosis of *Legionella* infection.
 - ⇒ results are positive during early infection and remain positive for several weeks or months and it is, therefore, not a test for cure.
- Polymerase chain reaction (PCR) using sputum or bronchoalveolar lavage specimen
 - ⇒ has high diagnostic accuracy (if available) and detects all *Legionella* species and serogroups
- The organism does not show up on Gram-staining.
- Cultures
 - ⇒ on buffered charcoal yeast extract (BCYE) agar.
 - ⇒ Sensitivity 20% to 95%; specificity 100%
- Chest x-ray: Diffuse reticular opacities are commonly seen

Management

- First line: fluoroquinolones or macrolides
 - ⇒ Fluoroquinolones: levofloxacin (preferred), ciprofloxacin, or moxifloxacin,
 - ⇒ Macrolides: Azithromycin (preferred), clarithromycin or erythromycin.
- Second line
 - ⇒ Tetracyclines: doxycycline

Pontiac fever

- Non-pneumonic Legionella infection
- causes a mild, self-limiting course of legionellosis without pneumonia.
- flu-like symptoms (e.g. fever, headache, and muscle ache)
- Not require antibiotic.

Mycoplasma pneumoniae

Pathogen

- Mycoplasma pneumoniae is a cause of atypical pneumonia, more closely related to gram positive bacteria.
- Because it lacks a cell wall, it is not visible on Gram stain and is not susceptible to antibiotics that inhibit cell wall synthesis, such as penicillins.

Epidemiology

- Most commonly affects younger patients (15-30 years).
- Accounts for 7% of all community-acquired pneumonias.
- Can occurs epidemic outbreaks, most commonly among persons living in close quarters, such as households, schools, and military facilities

Features

- URI and acute bronchitis are the most common (flu-like symptoms classically precede a dry cough)
- Systemic upset (arthralgia, haemolytic anaemia, erythema multiforme, Neurological, pericarditis/myocarditis, GIT, renal)
- Bilateral consolidation on x-ray

Complications → (Extra-pulmonary manifestations occur in ~10% of cases)

- Rash → Erythema multiforme, erythema nodosum
- Neurological : meningoencephalitis, Guillain-Barré syndrome, transverse myelitis
- · Cardiac: Myocarditis, Pericarditis
- Renal failure: acute glomerulonephritis
- Hepatitis
- **Haemolytic anaemia** (found in up to 50% of cases)
 - ⇒ the most common extra-pulmonary manifestations and is typically mild and selflimited.
 - ⇒ Presence of IgM antibodies (cold agglutinins) directed against the I antigen of the erythrocyte membrane → Spherocytes → Haemolysis → Features of haemolysis (direct Coombs' test, ↑reticulocyte counts, ↑unconjugated bilirubin, ↑LDH, ↓haptoglobins, fragmented red blood cells)

Mycoplasma pneumoniae → Serology is diagnostic

Diagnosis

- Mvcoplasma serology
 - ⇒ the "gold standard" diagnostic test
 - ⇒ 92% sensitivity and 95% specificity
 - ⇒ more sensitive than culture for detecting acute infection
- Positive cold agglutination test
 - ⇒ occur in only half of patients
- Chest X-ray
 - ⇒ might not correlate with the patient's condition → much worse than would be suggested by the clinical examination
 - ⇒ the commonest chest x-ray abnormality is bilateral interstitial infiltrate (90%)
- Nucleic acid amplification test (NAAT), such as polymerase chain reaction (PCR)
 - ⇒ Sensitivity is very high
 - ⇒ Faster than serology
 - ⇒ Cannot distinguish between active infection and asymptomatic carriage
 - ⇒ Causes of Positive PCR but negative serology tests
 - Asymptomatic carriage of M. pneumoniae (after disease, or during incubation period)
 - Immunocompromised patients, → no diagnostic antibody response.
 - Early successful antibiotics therapy.
- Culture
 - ⇒ rarely used for routine diagnosis
 - ⇒ sensitivity may be no more than 60%, but when positive, its specificity is 100%,
- · WBC can be normal

Mycoplasma pneumonia if allergic/intolerant to macrolides → doxycycline

High titer of cold agglutinins (IgM), which can agglutinate RBCs. *Mycoplasma* gets cold without a coat (no cell wall).

Management

- First line → macrolides (eg, azithromycin), tetracyclines (eg, doxycycline), and respiratory fluoroquinolones (eg, levofloxacin or moxifloxacin).
- Second-line → Tetracyclines such as doxycycline.

Prognosis

Most cases resolve spontaneously within a few weeks.

Indolent onset, concurrent URI symptoms (eg, rhinorrhea, pharyngitis, ear ache), and the presence of non-respiratory tract manifestations (eg, hemolysis) are suggestive *Mycoplasma pneumoniae*

Aspiration pneumonia

Definition

- a type of pneumonia that occurs as a result of oropharyngeal secretions and/or gastric contents aspiration
- also known as Mendelson syndrome

Risk factors

- ↓ level of consciousness (e.g. seizure, Alcohol use, stroke, post-anaesthesia) → impaired gag or swallowing reflex → aspiration occurred several weeks earlier.
- Gastroesophageal reflux disease, esophageal motility disorders, dysphagia.
- poor oral hygiene

Features

- Immediate symptoms: bronchospasms, crackles on auscultation, hypoxemia with cyanosis
- · Late symptoms: fever, shortness of breath, cough with foul-smelling sputum

Site of aspiration

- · which lung?
 - ⇒ Due to the angle of the bronchi, the right lung is more commonly affected by aspiration than the left lung.
 - ⇒ The right mainstem is more vertical and wider than the left mainstem bronchus.
- Which lobe?
 - ⇒ Depends on patient's position during aspiration:
 - in a patient who aspirates while recumbent (lying down):

- superior segment of the right lower lobe (most common site of aspiration)
- in a patient who aspirates while sitting upright:
 - posterior basal segment of the right lower lobe

Organisms

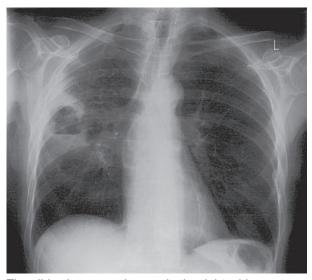
- Anaerobes and <u>Gram-negative</u> organisms are the usual organisms in abscesses following aspiration.
- Sputum or tracheal Gram stain reveals mixed flora.

Complications

- lung abscess and empyema
 - ⇒ air-fluid level is characteristic of a lung abscess.

Treatment

- Combination of antibiotics → Cefuroxime + Metronidazole
- If the patient is allergic to penicillin or cephalosporin → Vancomycin + Metronidazole



The slide shows an abscess in the right mid-zone.

<u>Psittacosis (Chlamydia psittaci pneumonia)</u> (<u>Atypical pneumonia</u>)

Exposure to an ill bird and a rash (Horder's spots) are pathognomonic

Definition

 Psittacosis is a disease caused by Chlamydia psittaci, an obligate intracellular organism, transmitted to humans from birds., induces prominent systemic manifestations and some respiratory.

Pathogenesis

- Humans are usually infected by inhalation of organisms in dried feces or in bird feather dust.
- Pet owners, vets and zoo keepers are most at risk.
- The incubation period is usually 5 to 14 days.

Diagnosis

- typical clinical features (fever, headache, myalgias, dry cough) in a patient with a history of bird contact
- In a patient presenting with pneumonia, severe headache, splenomegaly, and failure to respond to beta-lactam antibiotics may be other clues to the diagnosis.
- Serology: (e.g. microimmunofluorescent antibody testing, or complement fixation assay)
 the most useful diagnostic test
- Abnormal LFTs in up to 50%.
- Chest X-ray: segmental or diffuse multi-lobar consolidation.
- Culture is discouraged since *C. psittaci* is highly infectious when cultured and is only performed in specialized laboratories.

Complications

Respiratory failure, hepatitis, endocarditis, and encephalitis.

Treatment

- 1st line: tetracyclines e.g. doxycycline
- 2nd line: macrolides e.g. erythromycin or azithromycin

Pseudomonas pneumonia

Overview

- P. aeruginosa is a common cause of gram-negative hospital-acquired pneumonia
- Community-acquired P. aeruginosa pneumonia occurs mainly in
 - ⇒ immunocompromised patients (eq. HIV, post-transplant, or neutropenic hosts)
 - ⇒ structural lung abnormalities (e.g. cystic fibrosis, bronchiectasis, COPD)
- Nosocomial or hospital-acquired infections should be suspected in patients with an onset of symptoms at least 48 hours after admission to the hospital.

Treatment

• Antibiotics used for the treatment of Pseudomonas aeruginosa infections

Class	Agent
Penicillin-beta-lactamase combinations	Piperacillin-tazobactam
Cephalosporins	Ceftazidime or Cefepime
Fluoroquinolones	Ciprofloxacin or Levofloxacin
Carbapenems	Meropenem, Imipenem

- Fluoroquinolones are the only class of antibiotics with antipseudomonal activity that have an oral formulation.
- The only antipseudomonal penicillin is piperacillin.

Hospital-acquired pneumonia (HAP)

Definition

 Hospital-acquired pneumonia (HAP): nosocomial pneumonia, with onset > 48 hours after admission

Prevalence

 The third most common hospital-acquired infection after urinary tract infections and wound infections.

Causes

- Gram-negative organisms are the most common causes, especially aerobic gramnegative bacilli, such as:
 - ⇒ Pseudomonas aeruginosa,
 - ⇒ Escherichia coli,
 - ⇒ Klebsiella pneumoniae, and
 - ⇒ Acinetobacter species.

Diagnosis

 A new and/or persistent alveolar shadowing on chest x-ray or CT scan confirms the diagnosis.

Treatment

 most commonly as combination therapy. A third generation cephalosporin with an aminoglycoside is the current British Thoracic Society (BTS) recommendation.

Choice of antibiotic

Antibiotics for adults aged 18 years and over (NICE guidelines, September 2019)			
Treatment	Antibiotic		
First-choice oral antibiotic if non-severe symptoms or signs, and not at higher risk of resistance (guided by microbiological results when available)	Co-amoxiclav		
Alternative oral antibiotics if non-severe symptoms or signs, and not at higher risk of resistance, for penicillin allergy or if co-amoxiclav unsuitable.	Doxycycline Cefalexin (caution in penicillin allergy) Levofloxacin		
First-choice if severe symptoms or signs (e.g. sepsis) or ↑ risk of resistance.	Piperacillin with tazobactam Ceftazidime Ceftriaxone Cefuroxime Meropenem Ceftazidime with avibactam Levofloxacin		
If suspected or confirmed methicillin resistant Staphylococcus aureus infection (dual therapy with a first-choice intravenous antibiotic)	Vancomycin Teicoplanin Linezolid (if vancomycin cannot be used)		

Pneumocystis Jirovecii pneumonia (PCP)

Pneumocystis jiroveci pneumonia - pneumothorax is a common complication

Pathogen

• Pneumocystis jiroveci is an ubiquitous, yeast-like fungus unicellular eukaryote.

Association

- PCP is the most common opportunistic infection in AIDS
 - ⇒ Pneumocystis jirovecii pneumonia is <u>unlikely</u> in a patient who has had a <u>CD4 count above 200 cells/mm3</u> in the preceding 2 months in the absence of other HIV-associated symptoms.
- Immunosuppressed patients, particularly after organ transplantation

Pathophysiology

- The organism is <u>confined to the alveolar space</u> of the lung and produces debris and cysts in the alveolar space with interstitial infiltration of lymphocytes and plasma cells.
 As a result, it can <u>cause profound disturbance of oxygen exchange</u> and fatal hypoxaemia if left untreated.
- The morphological appearance of *Pneumocystis jirovecii* infection in the lung →
 An interstitial pneumonitis with foamy intra-alveolar exudate

Features

- · Dyspnoea, dry cough, fever
- Exercise-induced desaturation
- Very few chest signs: The lungs are commonly clear on auscultation
- Pneumothorax is a common complication of PCP.

Investigation

- Lymphopenia is very suggestive of PCP with AIDS (and therefore low CD4 lymphocyte count).
- Lactate dehydrogenase raised in 90% of patients with PCP (but this can occur with other pulmonary diseases).
- Chest x-ray
 - Typically shows bilateral interstitial pulmonary infiltrates (diffuse ground-glass opacities)
 - ⇒ 30% have non-specific or inconclusive findings.
 - ⇒ 10-15% of patients with *PCP* have normal chest radiographs
- Bronchoalveolar lavage (BAL)
 - ⇒ often needed to demonstrate PCP
 - ⇒ silver stain shows characteristic cyst phase of the organism
 - ⇒ Spontaneously expectorated sputum should not be used for diagnostic studies because it has poor sensitivity for PCP. Use induced sputum instead

 $\textbf{\textit{Pneumocystis jiroveci} pneumonia} \rightarrow \textbf{\textit{Definitive diagnosis is by bronchial alveolar lavage with silver staining}}$

Management

- 1ST line : Co-trimoxazole
 - ⇒ should be given for 21 days in HIV, but can be shorter in other causes of immunosuppression.
 - ⇒ the preferred initial therapy during pregnancy
 - ⇒ Glucose 6-phosphate dehydrogenase deficiency (G6PD) levels should be checked prior to TMP-SMX, dapsone or primaquine use
- 2nd line: in severe cases or in patients who are intolerant of co-trimoxazole → IV
 pentamidine
- Steroids
 - ⇒ Reduces mortality and prevent lung damage in people with moderate-to-severe PCP.
 - ⇒ a **21-day** tapering course has been shown to be safe and effective.
 - ⇒ The severity is determined on the basis of arterial blood gas results.
 - severe PCP is defined by a room air arterial oxygen pressure (pO2) of less than 9 kPa (70 mmHg) or an arterial-alveolar O2 gradient that exceeds 4.5 kPa (35 mmHg).

Any patient with PaO2 <70 and A-a gradient >35 should be started on steroid therapy.

Prophylaxis

- All patients with a CD4 count < 200/mm should receive PCP prophylaxis (Cotrimoxazole is the preferred agent. Dapsone and inhaled pentamidine are also used.)
- Primary Pneumocystis prophylaxis should be discontinued if the patient responded to ART with an increase in CD4 counts ≥200 cells/mm³ for ≥3 months.

MRCPUK-part-1-January 2016 exam

HIV positive but poorly compliant with his antiretroviral therapy (ART). CD4: 180 cells/ml. oxygen saturations 97% on room air with a temperature of 38.1°C. He has coarse crackles on the right side of his chest. A chest x-ray shows consolidation of the right mid zone. What is the most likely causative organism?

- ⇒ Streptococcus pneumoniae
- (Whilst Pneumocystis jirovecii is of course associated with HIV, patients who are immunocompromised are more likely to develop infections due to the common pathogens which affect immunocompetent individuals. Streptococcus pneumoniae is therefore the most likely cause of community-acquired pneumonia in this patient. Pneumocystis jirovecii tends to present with very few chest signs and bilateral interstitial pulmonary infiltrates on chest x-ray)

Coronavirus disease 2019 (COVID-19)

Overview

- Caused by coronaviruses, SARS-CoV-2
- The transmission occurs mainly through respiratory droplets (particles are greater than 5-10 micrometers in diameter) from coughing and sneezing.
- The incubation period is 2-14 days.
- Host cell entry occurs by attachment of viral spike protein to angiotensin-converting enzyme 2 receptor on cell membranes.

Features

- · Most common: Fever, Fatigue, Dry cough
- Common: Shortness of breath, Loss of smell and/or taste
- Less common: Thromboembolic events (e.g., pulmonary embolisms)
- Complications include respiratory failure, hypercoagulability, shock, organ failure.

Cytokine storm:

- an excessive release of proinflammatory cytokines that causes hyperactivation of immune system and exaggerated immune response leading to multiorgan dysfunction.
- · Initial treatment with tocilizumab plus a glucocorticoid

Risk factors for severe illness

- Increasing age,
- · Obesity,
- Diabetes, hypertension, chronic kidney disease, and severe cardiopulmonary illness.

Pathogenesis

- In the normal lung, type II pneumocytes secrete pulmonary surfactant; this phospholipid
 coats the alveoli and keeps them open and available for gas exchange. The initial lung
 injury in COVID-19 infection may occur via loss of surfactant and alveolar collapse.
- A cytokine storm occurs when white blood cells (WBCs) release large numbers of inflammatory cytokines (eg, interleukin [IL]-1, IL-6) in response to the virus, leading to further WBC activation

Diagnosis

- RT-PCR (most common)
 - ⇒ The nucleic acid amplification test (NAAT) is the diagnostic test of choice for COVID-19. NAAT is performed using RT-PCR.
- Antigen and antibody tests are available (less accurate)
- Chest x-ray may be normal in early or mild COVID-19. Findings in COVID-19 pneumonia include bilateral or peripheral consolidation or opacities
- **CT scan** findings may include ground glass opacities and consolidations, especially in the lung periphery

Management

- Cough
 - ⇒ Avoid lying on the back
 - ⇒ Use simple measures first, e.g. honey.
 - ⇒ If it is distressing → Consider short-term use of codeine linctus, codeine phosphate tablets or morphine sulfate oral solution in people 18 years and over to suppress coughing

Breathlessness

- ⇒ Identify and treat reversible causes of breathlessness, for example, pulmonary oedema, pulmonary embolism, chronic obstructive pulmonary disorder and asthma.
- ⇒ encouraging relaxation and breathing techniques, and changing body positioning
- ⇒ If hypoxia is the likely cause of breathlessness: consider a trial of oxygen therapy
- ⇒ Consider continuous positive airway pressure (CPAP) when:
 - hypoxaemia not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, and escalation to invasive mechanical ventilation would be an option but it is not immediately needed, or it is agreed that respiratory support should not be escalated beyond CPAP.
- ⇒ Consider using high-flow nasal oxygen for people having continuous positive airway pressure (CPAP) when they need:
 - a break from CPAP, such as at mealtimes
 - humidified oxygen
 - weaning from CPAP.

Corticosteroids

- ⇒ Indication: people with COVID-19 who need supplemental oxygen.
- ⇒ 1st choice: dexamethasone. Hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable.

Combination of casirivimab and imdevimab

- ⇒ to people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative).
- ⇒ Not recommended for patients who have detectable SARS-CoV-2 antibodies (seropositive)

Remdesivir

- ⇒ Indication: hospitalised patient who are > 12 year old and weight ≥ 40 kg and need low-flow supplemental oxygen.
- ⇒ Not recommended for patient who need NIV or invasive mechanical ventilation.

• Tocilizumab: (Single dose)

- □ Indications
 - hospitalised with severe COVID-19 (need O2 and CRP ≥ 75 mg/litre)
 - no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.
- ⇒ Consider sarilumab if tocilizumab is unavailable or cannot be used

Medication not recommended to treat COVID-19.

Azithromycin, budesonide, colchicine, doxycycline

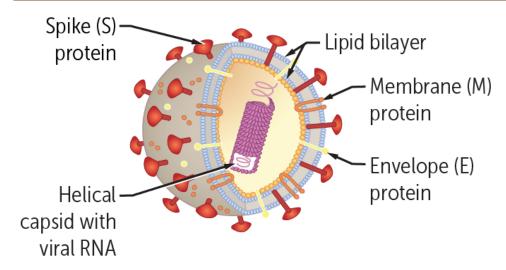
• Venous thromboembolism (VTE) prophylaxis

- ⇒ only for in hospital patients, consider a prophylaxis dose of low molecular weight heparin (LMWH) if the risk of VTE outweighs the risk of bleeding.
- ⇒ Do not base prophylactic dosing of heparin on levels of D-dimer.
- Antibiotics: Should not be used unless there is clinical suspicion of additional bacterial coinfection.
 - ⇒ Procalcitonin tests could be useful in identifying whether there is a bacterial infection.
 - ⇒ High C-reactive protein levels do not necessarily indicate whether pneumonia is due to bacteria or SARS-COV-2.
 - ⇒ Low C-reactive protein level indicates that a secondary bacterial infection is less likely.
 - ⇒ Do not use C-reactive protein to assess whether a person has a secondary bacterial infection if they have been having immunosuppressant treatment.

• Medicines for end-of-life care: opioid and benzodiazepine combination.

Remdesivir

- Remdesivir is a nucleotide prodrug of an adenosine analog.
- It binds to the viral RNA-dependent RNA polymerase
- It inhibits viral replication by terminating RNA transcription prematurely.
- Adverse Effects:
 † transaminase levels & prothrombin time (Liver function tests and prothrombin time tests should be performed for all patients before they receive remdesivir).



COVID-19 enters the lungs via type II pneumocytes.

Tocilizumab

- Mode of action
 - ⇒ Antagonizes the IL-6 receptor, which leads to a reduction in cytokine and acute phase reactant production.
- Common adverse effects (>10%)
 - ⇒ Neutropenia
 - ↑ liver enzyme
 - ⇒ ↑ serum cholesterol

Treatment of COVID-19 in pregnant patients

Initial management

- 1. Oxygen titrate supplemental oxygen to keep sats >94%
- 2. Thromboprophylaxis prophylactic LMWH dose according to weight
- 3. Corticosteroids if oxygen dependent give for a total of 10 days
 - a. Oral prednisolone 40mg OD; or
 - b. IV hydrocortisone 80ma BD
- If steroids used for fetal lung maturation use Dexamethasone 12mg IM 24 hourly (2 doses) followed by either (a) or (b) above for 10 days

Clinical deterioration

- Increased O2 requirements: O2 sat<93, RR > 22
 - ⇒ Give tociluzimab (or sarilumab if unavailable) if needing escalation of care and/or if CRP>75
 - ⇒ Check COVID-19 antibodies, if negative consider 2.4g Ronapreve IV once (RONAPREVE contains the active ingredients casirivimab and imdevimab.)

Discharge

- Thromboprophylaxis for at least 10 days
- Encourage COVID19 vaccination: can be given 28 days following recovery
- Advise: if given tocilizumab/sarilumab, be aware of an increased risk of infection without typical signs for several months.

Aspergillosis: Types

Overview

- Aspergillosis is the collective term for diseases caused by mold species in the genus Aspergillus.
- Most common: Aspergillus fumigatus and Aspergillus flavus
- Transmission: airborne exposure to mold spores

	АВРА	Chronic pulmonary aspergillosis (e.g. Aspergilloma)	Invasive aspergillosis
Main features	Asthmatic symptoms	Hemoptysis, shortness of breath	Dry cough, septic shock, multi- system involvement
Laboratory tests	 ↑ IgE levels Eosinophilia ↑ ESR Positive Aspergillus antigen skin test 	Positive Aspergillus IgG serology	 Positive galactomannan antigen test: (galactomannan is a protein found in Aspergillus cell wall). Positive 1,3-β-D glucan test Septate hyphae on tissue biopsy
Chest x-ray and CT	 Bronchiectasis Pulmonary infiltrates 	 Mobile fungus ball (demonstrated by moving the patient from a supine position to a prone or lateral recumbent position) Monod sign: a peripheral air crescent around a fungus ball in a preexisting lung cavity The upper lobe is mostly 	Multiple nodules Halo sign: hemorrhagic ground glass opacities around nodules

		affected	
Treatment	Oral prednisone if severe Itraconazole if recurrent	 Surgical resection (e.g., lobectomy) Itraconazole OR voriconazole (should be used preoperatively and postoperatively) 	IV voriconazole

The most important diagnostics for the different aspergillosis types are:

- ABPA: increased IgE and eosinophil count.
- Aspergilloma: positive culture or serology and fungus ball seen on chest imaging.
- Invasive aspergillosis: positive culture or biopsy showing septate hyphae.

Allergic bronchopulmonary aspergillosis (ABPA)

In the exam questions often give a history of bronchiectasis and eosinophilia.

Definition

- ABPA results from an allergy to Aspergillus spores (<u>Type I hypersensitivity</u> to Aspergillus fumigatus).
- a hypersensitivity reaction caused by exposure to Aspergillus that mostly occurs in patients with cystic fibrosis or asthma
- Aspergillus fumigatus is the most common airborne fungus causative organism for ABPA

Risk factors

Preexisting bronchopulmonary conditions (e.g., asthma, cystic fibrosis)

Features

- Bronchoconstriction: wheeze, cough, dyspnoea (clinical deterioration in asthma symptoms)
- Bronchiectasis (proximal)

Investigations

- Serum eosinophilia
- Raised IgE: helpful test, but not specific enough to establish the diagnosis.
- Aspergillus skin-prick test (the most specific investigation)
 - ⇒ Positive radioallergosorbent (RAST) test to Aspergillus.
 - ⇒ Immediate (type I) reactions occur in virtually all patients with ABPA following intradermal injections of *Aspergillus fumigatus* extracts, with only 16% developing delayed (type IV) reactions.
 - ⇒ An early positive skin-prick test for Aspergillus fumigatus is the most specific to (ABPA).
 - ⇒ Positive skin-prick tests reflect antigen-specific IgE.
- Positive IgG precipitins (not as positive as in aspergilloma) in 70% of patients.
 - ⇒ <u>Precipitins (IgG) are more usual with an aspergilloma</u>, but may be positive in ABPA or in up to 10% of patients with asthma.
- Pulmonary infiltrates on CXR. Lobar collapse can also occur, due to mucus plugging.

Allergic bronchopulmonary aspergillus: both of the following must be present to confirm the diagnosis:

- Aspergillus skin test positivity or detectable IgE levels against aspergillus fumigatus and
- Elevated total serum IgE concentration.

Management

- First line →steroids (prednisone)
- Second line → add itraconazole or voriconazole
 - Itraconazole leads to significant reductions in corticosteroid dose, decreases IgE levels, greater resolution of pulmonary infiltrates, and improves exercise tolerance.

Aspergilloma

The clue can be a lack of improvement with broad spectrum intravenous antibiotics, haemoptysis and chest X-Ray findings.

Definition

An aspergilloma is a mycetoma (mass-like fungus ball) which often colonises an
existing lung cavity (e.g. secondary to tuberculosis, lung cancer, cystic fibrosis or
emphysema)

Feature

- often asymptomatic
- cough
- haemoptysis in up to three quarters of patients (may be severe and fatal)
- Systemic symptoms of weight loss, lethargy and fever are less common.

Investigations

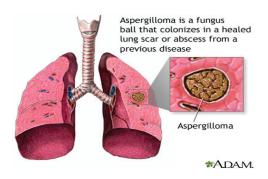
- chest x-ray containing a rounded opacity within a cavity often associated with a rim of air. These features are seen more clearly on CT.
- High titres Aspergillus precipitins (**IgG** antibodies) present in 95% of cases.

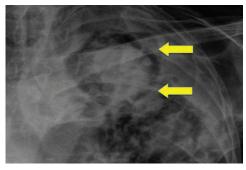
Treatment

- Surgery should be considered as a first-line option where erosion into a major vessel and massive haemoptysis is a possibility
- In case of massive haemoptysis the next appropriate management after transfusion and resuscitation- is → Angiography and embolisation, after that → lobar resection as the intervention of next resort

Aspergilloma should be considered in patients with chronic lung disease and radiographs showing intracavitary mass lesions.

Images





Invasive aspergillosis (IA)

Definition

• a severe form of *Aspergillus* infection with severe pneumonia and septicemia, most commonly occurs in immunocompromised individuals.

Risk factors

• **immunosuppression** (e.g., due to HIV/chemotherapy, after organ transplantation) or neutropenia (e.g., due to chronic granulomatous infection).

Features

Symptoms of active infection & haemoptysis.

Investigations

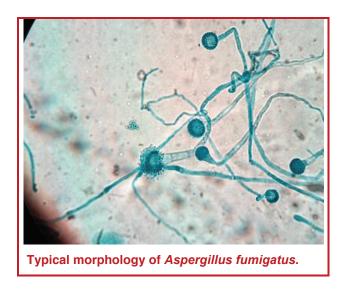
- the classical signs on CT scanning the 'halo sign' air crescent sign
- galactomannan test:
 - ⇒ Galactomannan is a component of the cell wall of the *Aspergillus* and is released during growth.
 - ⇒ Detection of galactomannan in blood by ELISA is used to diagnose invasive aspergillosis
- Silver staining shows → hyphae.
 - ⇒ Haematoxylin and eosin (H&E) stain does not stain most of the fungi, except the Aspergillus species.

Treatment

- 1st line **voriconazole:** start iv before oral (as oral 10 days to get therapeutic levels).
- 2nd line (If voriconazole is not tolerated); amphotericin B

Prognosis

Mortality vary from 40-90%





CT chest showed Aspergilloma

A slightly thick-walled left upper lobe cavity contains a rounded mass. A crescent-shaped airspace, termed the air crescent sign, separates the mass from the cavity wall. An aspergilloma can often be shown to move to the dependent position within its cavity

Invasive aspergillosis

- Invasive aspergillosis should be suspected in someone who is immunocompromised (neutropenia, steroids, HIV) with severe chest pain, highgrade fevers, and haemoptysis.
- The treatment of choice for invasive aspergillosis is voriconazole

Voriconazole $\to \uparrow$ risk of developing skin malignancy (malignant melanoma, squamous cell carcinoma)

Alpha-1 antitrypsin (A1AT) deficiency

Alpha-1 antitrypsin deficiency - autosomal recessive / co-dominant

Definition

 Alpha-1 antitrypsin (A1AT) deficiency is a common inherited genetic disorder characterized by the accumulation of defective alpha-1 antitrypsin enzyme

Genetics & Pathophysiology

- Alpha-1 antitrypsin: a protease inhibitor that is synthesized in the liver and protects cells from breakdown by neutrophil elastase (AAT neutralises neutrophil elastase, thereby preventing lung destruction.)
- The mode of inheritance: autosomal co-dominant
- Mutations in SERPINA1 gene, located on the long arm of chromosome 14 → dysfunctional (or absent) AAT
- A1AT deficiency is the most prevalent genetic disease in patients of finnish/scandinavian origin
- Alleles classified by their electrophoretic mobility M for normal, S for slow, and Z for very slow
- The serum levels of some of the common genotypes are:
 - ⇒ PiMM: 100% (normal)
 - ⇒ PiMS: 80% of normal serum level of A1AT
 - ⇒ PiSS: 60% of normal serum level of A1AT
 - ⇒ PiMZ: 60% of normal serum level of A1AT
 - ⇒ PiSZ: 40% of normal serum level of A1AT
 - ⇒ PiZZ: 10-15% (severe alpha 1-antitrypsin deficiency).
- Patients who manifest disease usually have PiZZ genotype
- Effect on the lungs: deficient AAT → uninhibited neutrophil elastase activity →
 destruction of the pulmonary parenchyma → panacinar emphysema
- Effect on the liver: accumulation of AAT in hepatocellular endoplasmic reticulum → hepatocyte destruction → hepatitis and liver cirrhosis

Features

- Pulmonary
 - Panacinar emphysema, most marked in <u>lower lobes</u> (2% of cases of emphysema)
 - ⇒ The interplay between the environmental and genetic factors determine its onset
 - ⇒ Patients usually present with increasing dyspnoea.

Hepatic

- ⇒ Hepatitis
- ⇔ Cirrhosis (15%)
- ⇒ Increased risk of hepatocellular carcinoma (HCC)

Investigations

- Serum: decreased antitrypsin protein levels
- · Electrophoresis: decreased alpha-1 peak
- Chest x-ray

 - ⇒ Widened intercostal spaces
 - ⇒ Hyperinflation and increased basilar radiolucency of both lungs with rarification of peripheral pulmonary vessels
- Chest CT
 - ⇒ Panacinar emphysema (in contrast to centriacinar emphysema in smokingrelated emphysema)
 - ⇒ Bronchiectasis
 - ⇒ Bullae
- Liver biopsy
 - ⇒ PAS-positive, spherical inclusion bodies in periportal hepatocytes
 - ⇒ Signs of cirrhosis

Management

- Avoid smoking
 - smoking is harmful to those with A1AT deficiency and can accelerate the progression of emphysema by 10 years.
- Supportive
 - ⇒ Preventive vaccination (e.g., influenza vaccine, pneumococcus vaccine)
 - ⇒ Symptomatic treatment (bronchodilators)
 - ⇒ Pulmonary rehabilitation (Physiotherapy)
- Intravenous alpha1-antitrypsin protein concentrates
- Surgery
 - ⇒ Volume reduction surgery
 - ⇒ Lung transplantation
 - ⇒ Liver transplantation → Results in correction of AAT deficiency (Considered for end-stage liver disease

Which form of lung disease develops typically in people with $\alpha 1$ -antitrypsin deficiency?

⇒ Emphysema

The diagnosis of AAT deficiency should be considered in all patients with emphysema under the age of 50 years.

Acute respiratory distress syndrome (ARDS)

Definition

 acute respiratory failure characterized by hypoxemia and bilateral pulmonary infiltrates that cannot be explained by heart failure or fluid overload.

Causes

- Sepsis (most common cause)
- Trauma
- Shock
- Massive transfusion (TRALI)
- Acute pancreatitis
- Hematopoietic stem cell transplantation
- Medication (e.g., salicylic acid, tricyclic antidepressants, bleomycin)
- Recreational drug overdose (e.g., cocaine)
- Primary damage to the lungs (Pneumonia, Aspiration, Inhaled toxins)

Pathophysiology

Tissue damage (pulmonary or extrapulmonary) → release of inflammatory mediators
 (e.g., interleukin-1) → inflammatory reaction → migration of neutrophils into alveoli →
 excessive release of neutrophilic mediators (e.g., cytokines, proteases, reactive oxygen
 species) → injury to alveolar capillaries and endothelial cells (diffuse alveolar damage)

Phases: diffuse alveolar damage lead to:

- Exudative phase:
 - ⇒ excess fluid in interstitium and on alveolar surface → pulmonary edema with normal pulmonary capillary wedge pressure (noncardiogenic pulmonary edema)
 → decreased lung compliance and respiratory distress
- Hyaline membrane formation:
 - ⇒ exudation of neutrophils and protein-rich fluid into the alveolar space → formation of alveolar hyaline membranes → impaired gas exchange → hypoxemia
 - ⇒ Hypoxemia → compensation through hyperventilation → respiratory alkalosis
 - ⇒ Hypoxemia → chronic hypoxic pulmonary vasoconstriction → pulmonary hypertension and right-to-left pulmonary shunt (increased shunt fraction)
 - ⇒ Damage to type I and type II pneumocytes → decrease in surfactant → alveolar collapse → intrapulmonary shunting
- Organizing phase (late stage):
 - ⇒ proliferation of type II pneumocytes and infiltration of fibroblasts → progressive interstitial fibrosis

What would one expect to see on a histological specimen of a lung from a patient who died of ARDS?

The presence of hyaline membranes is a hallmark of ARDS.

Features

- Symptoms: Acute dyspnea. Fever, cough, and chest pain may also be present.
- Signs: Tachypnea, cyanosis, diffuse crackles

What is the most consistent finding you would expect to see on arterial blood gases taken from patients with ARDS?

increased arterial-alveolar oxygen gradient.

ARDS is associated with:

- Increased elastic recoil.
- Low pulmonary artery wedge pressure.
- Low compliance.
- Restrictive lung disease

Berlin criteria for ARDS

- The Berlin criteria are the criteria most commonly used to define ARDS.
- All four of the following conditions must be met:
 - Acute onset: respiratory failure within one week of a known predisposing factor (e.g., sepsis, pneumonia)
 - 2) Bilateral opacities (on chest x-ray or CT)
 - Similar appearance to pulmonary oedema
 - Not sufficiently explained by pleural effusions, lobar or lung collapse, or nodules
 - 3) **Hypoxemia:** PaO2/FiO2 ≤ 300 mm Hg (measured with a minimum of 5 cm H2O PEEP)
 - Mild ARDS: PaO2/FiO2 = 201–300 mm Hg
 - Moderate ARDS: PaO2/FiO2 = 101–200 mm Hg
 - Severe ARDS: PaO2/FiO2 ≤ 100 mm Hg
 - Respiratory failure cannot be fully accounted for by heart failure or fluid overload.
 - Patients with ARDS have normal pulmonary capillary wedge pressure (PCWP) (<18 mmHg).

Management

- Admit all patients with ARDS to the ICU.
- Oxygenation
 - ⇒ Noninvasive ventilation: for hemodynamically stable, alert patients with mild ARDS.
 - ⇒ Endotracheal intubation: respiratory failure or rapid deterioration
- Lung-protective ventilation: to decrease the risk of ventilator-induced lung injury
 - ⇒ General initial settings include:
 - Low tidal volume (Vt 6–8 mL/kg): prevents alveolar distention
 - Low plateau pressure (PPlat ≤ 30 cm H2O): prevents barotrauma
 - PEEP > 5 cm H2O: allows for alveolar recruitment
 - ⇒ PEEP and FiO2 can be adjusted to recruit collapsed alveoli and improve oxygenation.
 - Oxygenation goal: PaO2 55–80 mm Hg or SpO2 88–95%
 - Avoid oxygen toxicity: use lowest FiO2 possible
- Identify and treat the underlying cause

- If the patient is on maximal ventilatory therapy but is still hypoxic & hypercapnic?
 - → Extracorporeal membrane oxygenation (ECMO) (connecting a patient's circulation to an external oxygenator and pump, via a catheter placed in the right side of the heart).
- Diuretics are NOT particularly effective, because the infiltrate of ARDS is primarily inflammatory.
- Glucocorticoids have NOT been shown to help patients in the acute phase of ARDS.

Acute respiratory distress syndrome (ARDS) diagnostic criteria:

- Abnormal x-ray,
- Respiratory failure < 1 week after a known or suspected trigger,
- Decreased PaO2/FiO2,
- Should exclude CHF or fluid overload as a potential cause of respiratory distress.

ARDS patient on mechanical ventilation

If the patient's blood gases reflect hypoxaemia and a slight respiratory alkalosis, (despite high FiO₂ settings and sufficient ventilation, his arterial oxygenation remains inadequate). What is the best next step?

- ⇒ Adding positive end-expiratory pressure (PEEP)
 - The ventilator strategy should employ a relatively high level of PEEP.
 - Generally, oxygenation may be improved by further increasing the FiO₂ or by adding PEEP.
 - High FiO₂ is contraindicated due to the risk of pulmonary oxygen toxicity.
 Thus, the goal in managing mechanically ventilated patients should be to keep the FiO₂ below 40% at all times.
 - The patients FiO₂ may need to be reduced soon- if more than 40% in order to avoid pulmonary oxygen toxicity, but this should be accomplished by <u>first increasing oxygenation by another means</u>, such as by increasing PEEP.
 - PEEP prevents alveolar collapse, directly counteracting the means by which ARDS causes hypoxaemia. It may also reopen some alveoli that have already collapsed.
- Which therapies has been shown to most likely decrease overall mortality of ARDS2
 - ⇒ Implementing a low tidal volume ventilation protocol (6 mL/kg based upon ideal body weight)
 - The target tidal volume is based on ideal, rather than actual body weight. Fat has no alveoli!
 - A target tidal volume of 6 ml/kg ideal body weight should be set maintaining plateau pressures of less than 30 cmH2O

The two main ventilator methods used in the management of ARDS are:

- High positive end-expiratory pressure (PEEP)
- Low tidal volume ventilation (LTVV)

Altitude related disorders

Response to high altitude

- The arterial partial pressure of oxygen (PaO₂) decreases with altitude, resulting in progressive tissue hypoxia. The normal compensatory response to hypobaric hypoxia is termed acclimatization. Its main feature is increased ventilation.
- ↓atmospheric oxygen (PiO2) → ↓ PaO₂ → ↑ventilation → ↓Paco2 → respiratory alkalosis → altitude sickness (headaches, nausea, fatigue, lightheadedness, sleep disturbance).
- Chronic ↑ in ventilation.
- ↑Erythropoietin → ↑Hct and Hb (due to chronic hypoxia).
- ↑ 2,3-bisphosphoglycerate (2,3-BPG) (binds to Hb → shifts the oxygen-hemoglobin dissociation curve to the right → ↑O2 release).
- Cellular changes (†mitochondria).
- ↑Renal excretion of HCO3- to compensate for respiratory alkalosis (can augment with acetazolamide).
- Chronic hypoxic pulmonary vasoconstriction → ↑pulmonary vascular resistance → pulmonary hypertension, RVH.

Types

- There are three main types of altitude related disorders:
 - 1. acute mountain sickness (AMS), which may progress to
 - 2. high altitude pulmonary edema (HAPE) or
 - 3. high altitude cerebral edema (HACE).
- All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness (AMS)

• AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days.

Features

- ⇒ Headache
- ⇒ Nausea
- ⇒ Fatigue

Treatment

- ⇒ descent
- ⇒ generally a self-limiting condition. usually resolves by day 3 with rest and gradual acclimatization to the high altitude.

Prevention

- ⇒ gain altitude at no more than 500 m per day
- ⇒ acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS
 and has a supporting evidence base

High altitude cerebral oedema (HACE)

- Generally occur above 4,000m
- HACE presents with headache, ataxia, papilloedema
- Management
 - ⇒ descent
 - ⇒ dexamethasone

High altitude pulmonary oedema (HAPE)

- Generally occur above 4,000m
- · Presents with classical pulmonary oedema features
- **Management** (after descent)
 - ⇒ 1st line → High concentration O₂
 - ⇒ 2nd line → Nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V
 - All seem to work by reducing systolic pulmonary artery pressure

Acetazolamide

- Carbonic anhydrase inhibitor
- Causes HCO₃ wasting (prevents HCO₃ reabsorption in the proximal tubule) metabolic acidosis, and subsequent diuresis.
- Metabolic acidosis → hyperventilation (physiological response) → ↑oxygenation → prevent altitude sickness

Bronchiectasis

Bronchiectasis should be suspected in a patient with chronic cough producing large amounts of sputum

Definition

Permanent dilatation of the airways secondary to chronic infection or inflammation.

Causes

- Post-infective: (i.e., bacterial, viral, fungal)
 - ⇒ tuberculosis, measles, pertussis, pneumonia
 - ⇒ A history of previous whooping cough suggests bronchiectasis.
- Disorders of secretion clearance, mucous plugging or bronchial obstruction
 - ⇔ Cystic fibrosis (CF)
 - ⇒ Primary ciliary dyskinesia (PCD)
 - ⇒ Allergic bronchopulmonary aspergillosis (ABPA)
 - ⇒ Kartagener syndrome
 - φ α1-antitrypsin deficiency
 - ⇒ Smoking: associated with poor ciliary motility
 - ⇒ Lung cancer/foreign body
- Immunodeficiency (e.g., common variable immunodeficiency, hypogammaglobulinemia,
- Chronic inflammatory diseases (e.g., rheumatoid arthritis, Sjogren syndrome, Crohn disease)
- Yellow nail syndrome

Features

The most common findings on examination are crackles (75%) and wheeze (22%). Clubbing is only found in 2%.

 Chronic productive cough, with copious amounts of sputum (expectorating phleam on most days)

- Dyspnea
- · frequent chest infections
- haemoptysis
- Post nasal drip common (chronic sinusitis in around 30%)
- Tiredness many patients find this more troublesome than the productive cough
- Low Ventilation perfusion ratio leading to hypercapnia → Respiratory acidosis, and the body compensate by increasing heart rate and vasodilatation.

Diagnosis

- Chest X-ray
 - ⇒ The best initial test
 - ⇒ can be normal in 50% of patients (Bronchiectasis cannot be ruled out with a chest x-ray)
 - ⇒ Findings:
 - thickened and dilated bronchi, which produce tramline opacities and ring shadows "tram track" lines due to Inflammation and fibrosis of bronchial walls
 - Retained mucus might be seen as tubular opacities,
 - volume loss of the affected lobe.
 - Thin-walled cysts (i.e., dilated bronchi forming sacs), possibly with air-fluid levels
 - Late-stage bronchiectasis: honeycombing
- High-resolution computed tomography scan of the lungs (HRCT)
 - ⇒ The gold standard for diagnosis of bronchiectasis.
 - **⇒** Findings
 - tram track lines and honeycombing
 - 'signet ring' sign
 - increased broncho-arterial ratio (bronchus larger than neighboring pulmonary artery). The bronchus and artery should be the same size, whereas in bronchiectasis, the bronchus is markedly dilated.

Differential diagnosis

- Carcinoma of the lung:
 - Lung cancer can present with non-resolving respiratory infection with productive cough due to endobronchial obstruction by tumour, but there would be a much shorter duration of symptoms. Without treatment most patients would be dead within a year of the onset of lung cancer.



Chest x-ray showing tramlines, most prominent in the left lower zone



CT chest showing widespread tram-track and signet ring sign

Subtypes of Bronchiectasis

- Cylindrical bronchiectasis
 - ⇒ bronchi have a uniform calibre, do not taper and have parallel walls (tram track sign and signet ring sign)
 - ⇒ commonest form (47%)
- varicose bronchiectasis
 - ⇒ relatively uncommon (9.9%)
 - ⇒ beaded appearances where dilated bronchi have interspersed sites of relative narrowing
- cystic bronchiectasis (45.1%)
 - ⇒ severe form with cyst-like bronchi that extend to the pleural surface
 - ⇒ air-fluid levels are commonly present
- multiple types: ~ 24.3%

Management

Symptom control in non-CF bronchiectasis \rightarrow inspiratory muscle training + postural drainage

The mainstay of therapy for bronchiectasis is antibiotics and chest physiotherapy.

After assessing for treatable causes (e.g. immune deficiency) management is as follows:

- physical training (e.g. inspiratory muscle training) has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- · postural drainage
- antibiotics for exacerbations + long-term rotating antibiotics in severe cases
- · bronchodilators in selected cases
- Immunisations: Influenza and pneumococcal vaccinations are strongly recommended.
- surgery in selected cases (e.g. Localised disease that fails to resolve after I.V antibiotic)

Most common organisms isolated from patients with bronchiectasis

Bronchiectasis: most common organism → Haemophilus influenzae

- Haemophilus influenzae (most common)
- Pseudomonas aeruginosa
- Klebsiella spp.
- Streptococcus pneumoniae

Prevention

- Primary prevention:
 - ⇒ antibiotic control of bronchial and pulmonary infections in predisposed individuals
- Secondary prevention:
 - ⇒ long-term low-dose macrolide treatment (e.g., azithromycin) in patients with two or more bronchiectasis exacerbations within one year.

Cystic fibrosis (CF)

Genetics

- Autosomal recessive; defect in CFTR gene on chromosome 7; commonly a deletion of Phe508.
- The defective gene inhibits the body's ability to move salt and water in and out of cells →
 Deranged chloride transport → thick, viscous secretions in the lungs, pancreas, liver,
 intestine, and reproductive tract.

Children whose parents are both heterozygous carriers of cystic fibrosis have a 25% chance of being affected by the condition.

Epidemiology

- Occurs in 1 in 2500 live births.
- The carrier frequency in white populations is 1 in 25.
- the most common genetically inherited diseases in Caucasian individuals.
- Rare in patients of Afro-Caribbean and Asian origin.
- 10% of people with cystic fibrosis are not diagnosed until adult life.

Features

- Failure to thrive and delayed puberty (100%)
- Infertility
 - ➡ Male infertility occurs in 98% due to failure of development of the vas deferens (congenital bilateral absence of the vas deferens (CBVAD); therefore, the anatomic duct through which spermatozoa pass from the testes to the urethra is absent, resulting in obstructive azoospermia)
 - ⇒ Patients may have CBVAD and cystic fibrosis transmembrane conductance regulator gene (CFTR) mutation without symptoms of CF.
 - ⇒ Female subfertility secondary to viscid cervical secretions. (only a 20% will be infertile)

Pancreatic insufficiency

- ⇒ The most common (85%) almost always present in adult patients
- ⇒ Due to obstruction of the pancreatic ductules by thickened secretions.
- ⇒ Diabetes mellitus: occurs in > 65% of patients by age 25
 - treatment of choice is subcutaneous insulin. Calorie intake should not be restricted in CF patients, who are prone to malnutrition due to their pancreatic insufficiency.
- ⇒ Malabsorption (30%): steatorrhoea
- ⇒ Fat-soluble vitamin deficiencies (including vitamins A, D, E and K)

Respiratory

- ⇒ Recurrent chest infections (40%)
 - Clues to a diagnosis of cystic fibrosis rather than an alternative immunodeficiency would be manifestations in other organ systems (pancreatic disease or infertility).
- ⇒ Allergic bronchopulmonary aspergillosis (ABPA) is a recognised complication, occurring in 15% of adult CF patients
- ⇒ Pneumothorax is seen in up to 5% of patients over 10 years of age and approximately 50% recur.

Liver disease

- ⇒ By young adulthood, CF-associated liver disease develops in 30 % of those affected
- ⇒ Cholestasis due to defective CFTR protein on bile duct epithelial cells

Nasal polyps

While nasal polyps occur in adults secondary to recurrent episodes of rhinitis, nasal polyps in children should always raise the suspicion for cystic fibrosis.

Gastro-intestinal

- ⇒ Distal intestinal obstruction syndrome :
 - most common bowel complication in cystic fibrosis after Gastroesophageal reflux disease (GERD)
 - Occurs in 10-20% of patients with cystic fibrosis and incidence increases with age. About 80% of cases present for the first time in adults.
- ⇒ Rectal prolapse (in children) due to bulky stools
- ⇒ Constipation is common

Renal

- ⇒ Urinary stress incontinence
- ⇒ Renal calculi (incidence increases with age and 1 in 20 adults are affected).

Distal intestinal obstruction syndrome is the most common bowel complication in cystic fibrosis after **Gastroesophageal reflux disease (GERD)**

Diagnosis

Sweat chloride test

- ⇒ The most important diagnostic test
- ⇒ Sweat chloride ≥60 mmol/L is abnormal. The patient should undergo CFTR gene mutation testing to confirm the diagnosis (false negative in 1-2% of patients).
- ⇒ Sweat chloride ≤29 mmol/L is normal. This is sufficient to rule out CF.

- ⇒ Sweat chloride 30 to 59 mmol/L is intermediate. These patients should have repeat sweat chloride testing and *CFTR* sequencing.
- ⇒ sweat test is conducted using pilocarpine iontophoresis.(a direct acting muscarinic agonist)
- ⇒ Causes of false negative sweat test
 - nephrotic syndromes.
- ⇒ Causes of false positive sweat test
 - malnutrition
 - adrenal insufficiency
 - glycogen storage diseases
 - nephrogenic diabetes insipidus
 - hypothyroidism, hypoparathyroidism
 - G6PD
 - ectodermal dysplasia
- Genetic test (DNA analysis) → CFTR gene mutation → confirm the diagnosis
 - ⇒ Should be performed for patients with intermediate or positive sweat chloride results.

Management

Management of pulmonary disease

- Airway clearance techniques
 - ⇒ Chest physiotherapy and postural drainage, regular (at least twice daily)
 - ⇒ An airway clearance session generally begins with SABA therapy to open the airways, followed by mucolytics to thin the mucus, then airway clearance techniques.
 - ⇒ high-frequency chest wall oscillation is not recommended by NICE.
- Mucoactive agents
 - ⇒ 1st line: rhDNase (dornase alfa; recombinant human deoxyribonuclease)
 - ⇒ 2nd line: rhDNase and hypertonic sodium chloride or hypertonic sodium chloride alone.
 - ⇒ 3rd line: mannitol dry powder for inhalation
- Anti-inflammatory agents (e.g., macrolide antibiotics, ibuprofen, corticosteroids) are used to control inflammation in the airway
- Lumacaftor-Ivacaftor Combination
 - ⇒ Used by NHS but not recommended by NICE
 - \Rightarrow specifically targets the most common *CFTR* mutation, the Δ F508 mutation.
 - ⇒ Ivacaftor potentiates the opening of the CFTR chloride ion transport channel,
 - ⇒ Lumacaftor improves the conformational stability of ΔF508-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface.

Lung transplant

- Indications
 - ⇒ Evidence of pulmonary hypertension
 - ⇒ FEV1 <50% predicted and rapidly declining (eg, >20% relative decline in FEV1 within 12 months)
 - ⇒ **FEV1 <40%** predicted and BMI <18 (while working to improve nutritional status)
 - ⇒ **FEV1 <40%** predicted and any of the following markers of shortened survival:
 - >2 exacerbations per year requiring intravenous antibiotics

- Massive hemoptysis (>240 mL) requiring intensive care unit admission or bronchial artery embolization.
- Pneumothorax
- ⇒ FEV₁ <30% predicted
- ⇒ Any of the following, regardless of FEV1:
 - 6-minute walk test <400 meters
 - Hypoxemia (SpO2 <88% or PaO2 <55 mmHg, at rest or with exertion)
 - Hypercarbia (PaCO2 >50 mmHg, confirmed on arterial blood gas)
 - Pulmonary artery systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of tricuspid regurgitant jet
 - Any exacerbation requiring positive pressure ventilation

Factors that warrant earlier consideration for transplant referral

- ⇒ Female sex, especially those who are younger
- ⇒ Short stature (height <162 cm)
- ⇒ Liver cirrhosis or chronic kidney disease (may require consideration of multiple organ transplantation and may affect timing or choice of transplant center)

Absolute contraindications include

- ⇒ Sepsis
- ⇒ multiple organ dysfunction,
- ⇒ documented history of non-adherence to treatment,
- ⇒ patients colonised with *Burkholderia cepacia*
- ⇒ class III obesity (body mass index [BMI] 40 or above), and
- ⇒ refractory gastro-oesophageal reflux.

Recipient criteria

- ⇒ Age under 60 years
- ⇒ Life expectancy of less than 18 months
- ⇒ No underlying cancer or serious systemic disease

· Donor characteristics

- ⇒ The donor should have been under the age of 40.
- ⇒ The chest of the donor should be slightly smaller than that of the recipient.
- ⇒ A double lung transplant is usually performed because of the risk of chronic infection in the remaining lung.

Management of extra-pulmonary disease

Nutritional interventions

- ⇒ **High calorie** diet, including **high fat** intake
- ⇒ CF → Weight loss → ↑ risk of exacerbations & overall mortality. For that it's important to maintain a high calorie diet
- ⇒ the best way to manage diabetes in CF is insulin and high calorie diet to allow them to convert those calories into stored energy.
- ⇒ Vitamin supplementation

For malabsorption

- ⇒ First test for exocrine pancreatic insufficiency→ **stool elastase** (if abnormal) → pancreatic enzyme replacement.
- ⇒ If symptoms persist → acid suppression agent (H2 receptor antagonist or a proton pump inhibitor)

For distal intestinal obstruction syndrome

⇒ 1st line: diatrizoate meglumine and diatrizoate sodium solution (Gastrografin) (orally or via an enteral tube)

- ⇒ **2nd line**: iso-osmotic polyethylene glycol and electrolyte (PEG) solution (macrogols) (orally or via an enteral tube)
- ⇒ 3rd line: surgery
- ⇒ Prevention by: encourage drink plenty of fluids & pancreatic enzyme replacement therapy & regular stool-softening agent such as lactulose.

Liver disease

 \Rightarrow If liver function tests are abnormal \rightarrow ursodeoxycholic acid

Chest infections in cystic fibrosis

Organisms

- ⇒ Infants and young children become colonised by *Staphylococcus aureus* and then *Haemophilus influenzae*.
- ⇒ Pseudomonas aeruginosa is the commonest colonising organism in patients with cystic fibrosis after the age of 10 years.(40 – 80%)
- ⇒ Aspergillus colonisation is also common 19%.
- ⇒ Burkholderia cepacia
 - Gram-negative, aerobic, rod bacteria.
 - Occurs in 5–10% of patients.
 - Often multi drug resistant.
 - Associated with the worst prognosis
 - Infection is a relative contraindication to undergoing lung transplant due to its association with poor outcomes.

In cystic fibrosis, *Staphylococcus aureus* infections are more common in childhood while *Pseudomonas* infections become more common in late adolescence and adulthood.

Antibiotics

⇒ Acute exacerbations

• **Combination** of piperacillin-tazobactam, ceftazidime, meropenem **plus** one of the following: a fluoroquinolone, tobramycin, amikacin, or colistin.

⇒ Chronic Pseudomonas aeruginosa infection

- the commonest colonising organism in patients with CF after the age of 10 years.
- Azithromycin at the time of the first positive culture
- test for nontuberculous mycobacteria before initiating azithromycin.
 Azithromycin should not be given to patients infected with nontuberculous mycobacteria, because it may induce antibiotic resistance.
- chronic azithromycin may reduce the efficacy of inhaled or intravenous tobramycin.
- 1st line → nebulised colistimethate sodium
- 2^{nd} line \rightarrow nebulised aztreonam, or nebulised **tobramycin**

Tobramycin

- Aminoglycoside antibiotic
- Works by binding to a site on the bacterial 30S and 50S ribosome, <u>preventing formation of the 70S complex.</u> As a result, mRNA cannot be translated into protein → cell death
- · Side effects:
 - ⇒ Nephrotoxicity
 - ⇒ ototoxicity (generally irreversible).

Prognosis

 The median survival is now predicted to be at least 40 years for children born in the 1990s.

Occupational lung diseases

- Occupational asthma
- Extrinsic allergic alveolitis (EAA)
- Pneumoconiosis
- Asbestos and the lung
- Pleural mesothelioma
- Silicosis
- Berylliosis
- Coal workers' pneumoconiosis (CWP)

Occupational asthma

Isocyanates are the most common cause of occupational asthma

Serial peak flow measurements at work and at home are used to detect occupational asthma

Overview

- Occupational asthma is a variable airflow obstruction attributable to a particular occupational exposure and not due to stimuli outside the workplace.
- Should be suspected and evaluated in every patient with adult-onset asthma. 5 to 25 % of all adult-onset asthma cases are occupationally related.
- · Occurs more frequently in atopic persons and smokers.

Causes

- Exposure to the following chemicals are associated with occupational asthma:
 - ⇒ **Isocyanates the most common cause**. (e.g. occupations include spray painting and foam moulding)
 - ⇒ Metals (Platinum salts, Aluminium, Chrome, Manganese, Nickel, Zinc)
 - ⇒ Disinfectant and preservatives (glutaraldehyde, chlorhexidine, formaldehyde)
 - ⇒ Flour
 - ⇒ Proteolytic enzymes

Diagnosis

- Confirmation of asthma
 - \Rightarrow Spirometry before and after bronchodilator \rightarrow reversibility of airflow limitation.
- Determine occupational relationship
 - ⇒ Symptoms become better at weekends / when away from work.
 - ⇒ Serial PEFR measurement at work and at home is a useful diagnostic test to assess a workplace contribution
 - ⇒ Skin test reactivity or immunoassay for specific immunoglobulin E (IgE) can identify sensitization to known occupational sensitizers.

Management

- Reduction of further exposure to the allergen.
 - ⇒ Change the Job if possible
 - Changing the pattern of the particular duties.
 - ⇒ An alternative is to use industrial respirators, which filter out 98-99% of respirable dust from the ambient air.
- Corticosteroid

Occupational asthma should be suspected in all adult patients with asthma.

<u>Hypersensitivity pneumonitis (HP) (also called extrinsic allergic alveolitis)</u>

Saccharopolyspora rectivirgula causes farmer's lung, a type of EAA

Aspergillus clavatus causes malt workers' lung, a type of EAA

Definition

 an immunologic reaction occurring within the pulmonary parenchyma caused by hypersensitivity to an inhaled agent, such as microbial, avian, animal antigens and, less commonly, organic compounds.

Pathophysiology

- Acute HP is predominantly mediated by antigen-antibody complex formation (type III hypersensitivity)
- Subacute and chronic HP result from an interplay of T helper (Th 1), T17, and T regulatory lymphocytes leading to lymphocyte infiltration and granuloma formation (delayed hypersensitivity) (type IV).
- Despite its name, EAA is not allergic and therefore features associated with allergy and type I reactions do not tend to occur in EAA (ie wheeze, immediate symptoms, raised IgE, positive skin-prick test, eosinophilia of blood or sputum).
- characterised <u>histologically</u> by:
 - Alveolar destruction and interstitial inflammation.
 - ⇒ Non-caseating granulomas
 - ⇒ **Asteroid bodies** may be found in or adjacent to the granulomas.

Examples

- Farmer's lung:
 - Caused by spores of Saccharopolyspora rectivirgula (formerly Micropolyspora faeni)
 - ⇒ The commonest occupational hypersensitivity pneumonitis
 - Contaminated hay is the most common source of Saccharopolyspora rectivirgula
 - ⇒ Serum precipitating antibodies to Saccharopolyspora rectivirgula is the most useful diagnostic test (found in 75-100% of cases during an acute episode).

Disease	Antigen Source
Farmer's lung (The commonest occupational hypersensitivity pneumonitis)	spores of Saccharopolyspora rectivirgula (commonly from Contaminated hay)
Bird fanciers' lung	avian proteins
Malt workers' lung	Aspergillus clavatus
Mushroom workers' lung	thermophilic actinomycetes
Maple bark stripper's lung	Cryptostroma corticale
Cheese washer's lung	Penicillium casei

Features

- **Acute**: occur 4-8 hrs after exposure, SOB, dry cough, fever. Symptoms subside after 12 hours to several days (in the absence of additional exposure)
- **Chronic** (months after continuous exposure): exertional shortness of breath and pulmonary fibrosis **(typically upper-lobe)**.

A recurrent common cold with an irritating cough and fever may indicate hypersensitivity pneumonitis.

Investigation

- Chest x-ray
 - ⇒ Upper/mid-zone fibrosis.
 - ⇒ Nodular shadowing or ground glass appearances.
 - ⇒ Classically show diffuse air-space consolidation
- Pulmonary function test: restrictive pattern
- Bronchoalveolar lavage (BAL) → lymphocytic predominance
- Blood cell count → NO eosinophilia
- Serology → Circulating IgG precipitins
 - ⇒ Demonstration of precipitating antibodies (precipitins) in the patient's serum to the causal antigen.
 - ⇒ Have a high false negative rate (positive results can be seen in exposed, but asymptomatic individuals). Positive serum avian precipitins are not diagnostic of HP, and only suggest the patient has had exposure to birds.
- Histopathology: Noncaseating granulomas with lymphocytes and polynuclear giant cells

Treatment

- Removal of exposure to the antigen (change of job plan)
 - ⇒ The optimal management
 - ⇒ Symptoms may settle within 12 hours of removal of the antigen.
- Prednisolone

MRCPI-part-1-january-2016: A 65-year-old farmer presents with SOB and wheeze progressively worsening over the past 6 months. He is a smoker, and has two daughters with asthma. There was obvious wheeze and coarse end-inspiratory crackles on examination of the chest. A chest X- ray shows diffuse non-specific changes consistent with lung disease.

Which would be the next most appropriate investigation?

- **⇒** Spirometry and reversibility
 - This man either has asthma, chronic obstructive pulmonary disease or farmer's lung
 - Spirometry and reversibility would be the investigation of choice.
 - ❖ A restrictive defect would support a diagnosis of farmer's lung;
 - an obstructive defect with reversibility would support a diagnosis of asthma.
 - respiratory obstruction without reversibility would support a diagnosis of COPD.

Pneumoconiosis

Definition

A group of chronic lung diseases caused by exposure to a mineral dust or a metal.

Types

- Asbestosis
- Silicosis
- Coal workers' pneumoconiosis (black lung disease), and
- · chronic beryllium disease.

Risk factor

- In silicosis and coal workers' pneumoconiosis, exposure should be (at least 10 and usually 20 or more years prior to radiographic changes) (the cumulative dose inhaled).
- Beryllium is immunologically mediated with a strong genetic component, so that the
 typical dose response demonstrated with the other pneumoconioses is not seen (NO
 need for cumulative dose)

Features

- Asymptomatic in early stages
- Dyspnoea on exertional dyspnoea, dry cough

Diagnosis

- Chest x-ray
 - The presence of non-calcified, multiple (in the hundreds), rounded opacities in the upper zones is highly suggestive of silicosis or coal workers' pneumoconiosis.
 - ⇒ Asbestosis typically causes lower lobe fibrosis.
- High-resolution CT (HRCT) scan chest
 - ⇒ more sensitive than CXR in identifying interstitial fibrosis.
- · Individuals with silicosis should be tested for TB.

Treatment

- Smoking cessation + removal of occupational exposure
- Patients with respiratory failure → referral for lung transplant
 - ⇒ Absolute contraindications include:
 - Associated other incurable advanced disease
 - Addictions including tobacco,
 - Lack of social support
 - Documented non-adherence to medical therapy.

Exposure to isocyanates most likely associated with squamous-cell carcinoma of the bronchus.

Hard metal lung disease (Cobalt exposure)

- A worker in the hard metal industry, comes with progressive dyspnea. Chest X-ray shows diffuse interstitial fibrosis bilaterally. what is the typical cellular component found in a bronchoalveolar lavage (BAL) of this patient?

 - ⇒ Persons working in the **hard metal industry** are prone to develop a condition called hard metal lung disease.
 - ⇒ The pathological diagnosis is giant cell interstitial pneumonia (GIP).

Asbestos and the lung

The most common malignancy associated with asbestosis is bronchogenic carcinoma, not mesothelioma

Risk of asbestos exposure

- · Ship building,
- car manufacture,
- · boiler making and
- plumbing industries

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma.

Pleural plaques

- The most common form of asbestos related lung disease
- occur after a latent period of 20-40 years.
- rarely cause symptoms
- · benign and do not undergo malignant change.
- CXR may shows calcification on both hemidiaphragms which are most likely to be pleural plaques from previous asbestos exposure.
- Do not require long term follow up

Asbestosis (asbestos-related pulmonary fibrosis)

- Diffuse interstitial fibrosis secondary to asbestos inhalation
- Slowly progressive, the latent period is typically 15-30 years.
- The severity of asbestosis is related to the length of exposure. This is in contrast to mesothelioma where even very limited exposure can cause disease.
- Typically causes lower lobe fibrosis.
- Pleural effusions and supradiaphragmatic pleural plaques are common findings on x-ray in patients with asbestosis.
- Biopsy is not mandatory as the diagnosis can be made on clinical and radiological grounds.
- On microscopic examination, asbestosis is marked by interstitial fibrosis with the presence of characteristic asbestos bodies and ferruginous bodies.
- Resistant to treatment with immunosuppressive therapy.
- The risk of lung cancer is raised more than 50-fold in smokers with asbestos.

Pleural mesothelioma

Definition

Malignant tumor of mesothelial cells of pleura

Epidemiology

• More common in male than female (3:1)

Risk factors

- Asbestos (20- to 40-year after exposure)
- Smoking, alcohol, and diet do not increase the risk.

 Loss of material from chromosome 22 is commonly seen in mesothelioma cell lines

Features

- History of asbestos exposure in 85-90%, latent period of 20-40 years
- Dyspnoea, weight loss, chest wall pain
- · pleural effusion

Diagnosis

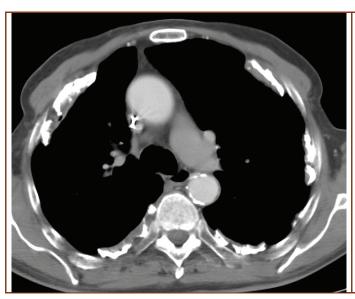
- Chest x-ray showing either a pleural effusion or pleural thickening
- CT chest with contrast → the best next step after chest x-ray
 - ⇒ Multiple nodular pleural lesions (pleural thickening)
- Pleurocentesis (If a pleural effusion is present) for biochemistry and cytology
 - ⇒ <u>exudative</u> and hemorrhagic pleural fluid.
 - ⇒ cytology is only helpful in 20-30% of cases
 - ⇒ don't rely on cytology alone to confirm the diagnosis
- Thoracoscopy biopsy
 - the most important investigation to confirm the diagnosis.
 - ⇒ used to investigate cytology negative exudative effusions as it has a high diagnostic yield (around 95%).
 - ⇒ Psammoma bodies are seen on histology
- Positron emission tomography (PET) with CT (PET-CT) as the initial staging after histopathological confirmation of the diagnosis.

Management

- · Radiation, with or without chemotherapy
- Surgery (pleurectomy or pneumonectomy) in severe cases if operable

Prognosis

- Poor. The median survival after diagnosis is 1- 2 years
- Bronchogenic carcinoma is the most common malignant pulmonary tumor in patients with asbestosis
 - ⇒ Bronchogenic carcinoma is more common than mesothelioma
 - The <u>lack of smoking history</u> along with previous asbestos exposure and signs of a <u>pleural effusion</u> make malignant mesothelioma more likely than bronchial carcinoma.



This patient has mesothelioma. The calcification of the pleura is a hallmark of asbestos exposure.



CT scan showing mesothelioma

- There is a large rind of soft tissue related to the left chest wall.
- This is a malignant process as there is destruction of the associated rib.

Silicosis

Overview

- a pneumoconiosis that results from the inhalation of silica dust.
- Affects upper lobes
- Increases susceptibility to tuberculosis.
- Risky jobs
 - ې Silicosis can affect anyone involved in quarrying(المحاجر), carving, mining (المحاجر), tunneling (حفر الانفاق), grinding(طحن) or sand-blasting (نسف), if the dust generated contains quartz.
 - ⇒ manufacture of toilet bowls, sinks(مغاسك), and ceramics;
 - ⇒ hydraulic fracking while drilling for gas and oil.

Pathophysiology

Macrophages activated by silica (quartz) →release fibrogenic cytokines → causes
inflammation and scarring in the form of nodular lesions in the upper lobes of the lungs.

Classifications

- Acute silicosis
 - ⇒ The most severe form
 - ⇒ develops a few weeks to 5 years after exposure due to very heavy exposure.
 - ⇒ Chest X-ray shows appearances resembling pulmonary oedema.
 - ⇒ Treatment 1st line → whole lung lavage.
- Accelerated silicosis
 - ⇒ Develops 5–10 years after first exposure due to ess heavy exposure
- Simple nodular silicosis
 - ⇒ the most common type
 - ⇒ resulting from long-term exposure (10 -30 years) to relatively low concentrations
 of silica dust
 - ⇒ radiographic nodular changes similar to coal-worker's pneumoconiosis,

Differential diagnosis

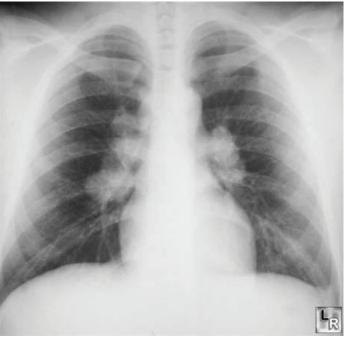
- Simple nodular silicosis differs from coal-worker's pneumoconiosis in that :
 - ⇒ the lesions tend to be larger (3-5 mm)
 - ⇒ and it is progressive even after dust exposure ceases

Diagnosis

- 'Egg-shell' calcification of the hilar lymph nodes is pathognomonic for silicosis;
- Pulmonary function test → usually reveal mixed obstructive / restrictive picture
- · biopsy shows silica particles (birefringent) surrounded by collagen

Complications

- ↑ susceptibility to TB (silica is toxic to macrophages)
- ↑ incidence of primary lung cancer
- ↑ risk of connective-tissue disease, vasculitides, (COPD), and chronic renal failure.



The chest radiograph shows **"eggshell" calcification** of the hilar lymph nodes, as seen with **silicosis.**

Berylliosis

Overview

- Jobs at risk: aerospace or nuclear industry workers, manufacture of electronics, manufacture of heat-resistant ceramics, dental prostheses, and metal products
- Characterized by the presence of noncaseating granulomas in the lungs, nodular infiltrates, and enlarged lymph nodes (resembles sarcoidosis)
- The presence of glutamic acid at position 69 of the HLA-DP1 beta chain is strongly associated with chronic beryllium disease.

Diagnosis

- Chest radiograph shows hilar adenopathy or reticular and nodular lung opacities.
 - ⇒ Chest x-ray → linear opacities.
 - ⇒ silicosis and coal workers' → rounded opacities
- Blood beryllium lymphocyte proliferation test (BeLPT)
 - the initial diagnostic test of choice for patients with clinical or radiographic evidence of lung disease
- Beryllium lymphocyte proliferation test (BeLPT)
 - ⇒ Sensitive test that identifies individuals sensitised to beryllium.
 - ⇒ Bronchoscopic lavage fluid may be positive when the blood test is negative.
 - ⇒ The occurrence of a positive BeLPT without granulomas on histology is an indication of sensitisation to beryllium and absence of chronic beryllium disease.

- Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), endobronchial biopsy, and transbronchial biopsy.
 - the next test for patients with a positive blood BeLPT or a strong clinical suspicion despite a negative blood BeLPT
 - ⇒ To obtain an adequate number of cells for BeLPT
 - ⇒ biopsy → granulomas present

Diagnosis of berylliosis

- requires all three of the following findings:
 - 1) history of beryllium exposure,
 - 2) positive BeLPT,
 - 3) presence of noncaseating granulomas and/or mononuclear cell infiltrates on lung histopathology.
- A clinical diagnosis can also be made based on a positive BAL BeLPT and lymphocytosis (>20 %) in bronchoalveolar lavage fluid.

Complications

† risk for primary lung cancer

Treatment

- · cessation of exposure to beryllium
- Acute and chronic berylliosis → Oral corticosteroid therapy (prednisone)

Coal workers' pneumoconiosis (CWP)

Pathology

- CWP results from inhalation and deposition of coal dust particles.
- prolonged exposure to coal leads to pulmonary macrophages becoming filled with carbon, known as carbon-laden macrophages ("dust cells")
- Affects upper lobes (high ventilation)

Types

- Simple CWP
 - ⇒ like smoking, can produce centrilobular emphysema
 - ⇒ Fine nodular opacifications (< 1 cm) in upper lung zone
 - ⇒ often asymptomatic and the diagnosis is an incidental finding on CXR.
- Complicated CWP (Progressive massive fibrosis)
 - **⇒** Exposure to dust of high silicon content
 - ⇒ Fine nodular opacifications 1-2 cm with progressive massive fibrosis
 - ⇒ Chest x ray: round masses, several centimetres in diameter (> 1 cm), sometimes up to 10 cm. may have necrotic centres.
 - ⇒ Chest CT: Mass-like areas of lung opacification associated with radiating strands are seen; the "sausage-shaped" mass is characteristic.
 - ⇒ Mixed obstructive and restrictive lung

Diagnosis

• Chest x-ray → small interstitial nodules in the upper and mid zones of the lung.

The presence of carbon-laden macrophages is the histologic hallmark of coal workers' pneumoconiosis.

Complications

- ↑ risk of connective-tissue disease and COPD
- ↑ Risk of Caplan syndrome (coal worker's pneumoconiosis that occurs with joint manifestations of rheumatoid arthritis.)
- NO association with lung cancer or TB

Coughing up of black sputum (melanoptysis) is pathognomonic of coal workers pneumoconiosis.

Although coal is mined from under the earth, the upper lobes of the lungs are primarily affected.

Caplan's syndrome

- . Coal workers pneumoconiosis associated with rheumatoid arthritis
- Typically bilateral, peripheral nodules 5 mm to 5 cm in size
- peripheral lung nodules with the histopathology of rheumatoid nodules develop on a background of pneumoconiotic opacities.
- In contrast to pneumoconiotic masses, they can develop rapidly, over a period of weeks, and may cavitate or calcify.

Primary ciliary dyskinesia (PCD)

Definition

 A rare autosomal recessive disorder characterized by absent or dysmotile cilia caused by a defect in the dynein arm of microtubules resulting in abnormal ciliary motion and impaired mucociliary clearance throughout the body.

Features

- Recurrent or persistent respiratory infections (which may lead to bronchiectasis)
- · Recurrent Sinusitis, and Otitis media
- Conductive hearing loss
- Male infertility (due to decreased sperm motility as a result of defective flagella)
- Reduced fertility in women and ↑ risk of ectopic pregnancy due to defective movement of the cilia in the fallopian tube
- In 50% of the patients, PCD is associated with situs inversus (**Kartagener's syndrome**): triad of situs inversus, recurrent sinusitis, and bronchiectasis

Differential diagnoses

- cystic fibrosis
 - ⇒ The diagnosis of CF is based on typical pulmonary and/or gastrointestinal tract manifestations and positive results on sweat test (pilocarpine iontophoresis).
 - ⇒ A negative sweat test is sufficient evidence to exclude CF.

Diagnosis

- Nasal nitric oxide (NNO) levels
 - ⇒ the most sensitive and specific screening test for PCD
 - Sensitivity of 97% and specificity of 90% for PCD.
 - ⇒ A low NNO (<100 parts per billion) should be followed up with confirmatory testing (nasal or bronchial brush biopsy for ciliary examination) because other conditions such as cystic fibrosis may present with low NNO.
 </p>
 - ⇒ A high NNO virtually excludes PCD
- Definitive diagnosis is usually based on identification of ciliary abnormalities on high speed videomicroscopy analysis (HSVA) or transmission electron microscopy (TEM).
 These tests require nasal or bronchial biopsy
- Genetic test for dynein arm mutations is difficult due to multiple phenotypes

Treatment

- · Reducing respiratory infections
 - ⇒ regular use of nebulized (hypertonic) saline, twice daily before airway clearance techniques; inhaled bronchodilator is administered prior to nebulized saline.
 - ⇒ Azithromycin maintenance therapy (250 mg for <40 kg or 500 mg for ≥40 kg, three times a week)

Kartagener's syndrome

primary ciliary dyskinesia (PCD) + situs inversus → Kartagener's syndrome

Definition

- Kartagener syndrome is a subtype of primary ciliary dyskinesia characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis.
- most frequently occurs in examinations due to its association with dextrocardia (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads')

Pathogenesis

- autosomal recessive mutation.
- dynein arm defect results in immotile cilia
 - ⇒ **dynein** is a protein found in Cilia and flagella of microtubule

Features

- Dextrocardia or complete situs inversus
 - ⇒ Situs inversus occurs in about half of people with Kartagener syndrome
- Bronchiectasis
- · Recurrent sinusitis
- Male infertility and female subfertility (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)
- Deafness
- Hydrocephalus.

H/O recurrent chest infections , situs inversus, and sperm sample shows nonmotile spermatozoa. The cause of this condition is most likely a mutation in the genes for which protein? \rightarrow Dynein

You can memorize the cause of Kartagener syndrome by thinking of Kartagener's restaurant that only has 'take-out' service because there is no dine-in (dynein).

Kartagener syndrome: triad of:

- 1. situs inversus,
- 2. chronic sinusitis, and
- 3. bronchiectasis.

Lung cancer: General overview

Epidemiology

- Second most common cancer (after breast cancer in women and prostate cancer in men).
- More common in males except for adenocarcinoma, which is more common in women

Risk factors

- Smoking
 - ⇒ increases risk of lung ca by a factor of 10
 - ⇒ Smoking and asbestos are synergistic, i.e. a smoker with asbestos exposure has a 10 X 5 = 50 times increased risk
 - ⇒ Up to 15% of lung cancers in patients who do not smoke are thought to be caused by passive smoking
- Occupational exposure
 - ⇒ Asbestos increases risk of lung cancer by a factor of 5
 - ⇒ Isocyanates occurs in chemical workers in the rubber industry → non-small-cell lung cancer , squamous-cell carcinoma
 - ⇒ Arsenic, radon, nickel
- Preexisting chronic obstructive pulmonary disease (COPD), tuberculosis, and idiopathic pulmonary fibrosis (IPF).

Coal dust is not a risk factor of lung cancer

Types of lung cancer

- Non-small cell lung cancer (NSCLC)
 - ⇒ 85% of all lung cancers
 - ⇒ Most, but not all patients will have a smoking history
 - ⇒ Less malignant than small cell lung cancer, less responsive to chemotherapy.
 - ⇒ The overall 5-year survival rate is about 15%
 - ⇒ Has main 3 subtypes:
 - Adenocarcinoma ≈ 40% of NSCLC cases
 - The most common form of lung cancer in non-smokers, women, and young adults
 - ❖ Typically located on the lung periphery → normal bronchoscopy.
 - May associate with Gynaecomastia.
 - Histology will show: glandular mucin-producing cells

- Squamous ≈ 30% of NSCLC cases
 - Typically, central (Squamous = Sentral)
 - Associated with ↑parathyroid hormone-related protein (PTHrP) secretion → hypercalcaemia
 - Cavitate (In 10% of cases)
 - Histology will show: Pleomorphic cells in cluster with keratin pearls and intercellular bridges
- Large cell carcinoma (10%-15%).
 - A diagnosis of exclusion. The cells belonging to this cancer will not have mucous, squamous differentiation, neuroendocrine properties, or small cell characteristics. Cells will be large with abundant amounts of cytoplasm, large nuclei, and prominent nucleoli.
 - Originates from an epithelial cell.
 - Most commonly grow in the periphery.
 - Highly anaplastic and poorly differentiated.
 - ❖ Associated ↑beta-hCG
 - Poorly responsive to chemotherapy and often require surgical excision.
 - Prognosis is generally poor.

Small cell lung cancer (SCLC)

- ⇒ Also known as "oat-cell carcinoma"
- ⇒ 15% of all lung cancers
- ⇒ Strongly associated with smoking
- ⇒ Usually centrally located
- ⇒ Most aggressive cancer which typically presents with a short history and 80–90% will have metastases at the time of presentation.
- ⇒ Very poor prognosis. median survival is 6–12 months.

Squamous cell cancer

Squamous cell and Small cell lung cancer are both Sentrally (Centrally) located.

Lung adenocarcinoma

- most common type in non-smokers
- peripheral lesion

Non-small cell lung cancer (NSCLC): adenocarcinoma VS squamous cell carcinoma

	Lung adenocarcinoma (AC)	Lung squamous cell carcinoma (SCC)
Location	Peripheral	Central
Characteristics	Most common type of lung	Strong association with
	cancer worldwide	smoking
	More common in women	Cavitary lesions arising from
	and nonsmokers	a hilar bronchus

	Prognosis is usually better than in other types of lung cancer	
Paraneoplastic features	Adenocarcinoma: HPOA → Clubbing	□ PTHrp →Hypercalcemia
Histology	Glandular tumor Mucin-producing cells (positive mucin staining)	Solid, epithelial tumor Intercellular bridges (desmosomes) Keratin pearls

Bronchioloalveolar carcinoma (BAC) is a pathological subtype of non-small cell lung cancer (NSCLC)

- Adenocarcinoma
- usually demonstrating a peripheral lesion.
- grow along the alveolar walls without actually destroying them.
- alveoli are often filled with mucin.
- The classic massive clear frothy sputum (bronchorrhoea) can be up to one litre a day.
- not resectable, poor prognosis.

Features

- Small tumours are often asymptomatic, so the majority of patients have either locally advanced or metastatic disease at diagnosis.
- Most common presenting symptoms are cough, chest pain, haemoptysis, dyspnoea, and weight loss.
- Regional adenopathy and compression of nearby structures may result in superior vena cava syndrome, hoarseness, and dysphagia.
- Obstruction of a central bronchus may result in postobstructive pneumonia

Referral

- Consider immediate referral for patients with:
 - ⇒ signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)
 - ⇒ stridor
- Refer urgently for chest x-ray for patients with any of the following:
 - ⇒ haemoptysis
 - □ unexplained or persistent (longer than 3 weeks): chest and/or shoulder pain, dyspnoea, weight loss, chest signs, hoarseness, finger clubbing, cervical or supraclavicular lymphadenopathy, cough, features suggestive of metastasis from a lung cancer (for example, secondaries in the brain, bone, liver, skin)
 - □ underlying chronic respiratory problems with unexplained changes in existing symptoms
- Refer urgently (for an appointment within 2 weeks) patients with:
 - ⇒ persistent haemoptysis (in smokers or ex-smokers aged 40 years and older)

- ⇒ a chest X-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)
- ⇒ a normal chest X-ray where there is a high suspicion of lung cancer
- ⇒ a history of asbestos exposure and recent onset of chest pain, shortness of breath or unexplained systemic symptoms where a chest x-ray indicates pleural effusion, pleural mass or any suspicious lung pathology

MRCPUK-part-1-january-2017: H/O Rapid progression (cough, lung mass and weight loss within 2 months) + paraneoplastic peripheral neuropathy. What is the most likely diagnosis?

⇒ Small-cell carcinoma. (Squamous cell carcinoma and adenocarcinoma are usually very slow growing).

Lung cancer: paraneoplastic features

Paraneoplastic features of lung cancer

- Squamous cell: PTHrp → Hypercalcemia
- Adenocarcinoma: HPOA → Clubbing
- Small cell:
 - ⇒ ↑ADH → **SIADH**
 - ⇒ ↑ACTH → Cushing syndrome
 - ⇒ Lambert-Eaton syndrome

Overview

- Paraneoplastic syndromes are a result of antibody generation from or against malignant cells attacking normal tissue.
- Paraneoplastic syndromes occur in 10% of patients with lung cancer
- Both non-small cell and small cell lung cancers are associated with Paraneoplastic syndromes, although they are more common with the small cell due to its neuroendocrine cell origin.

Paraneoplastic features associated with non-small cell lung cancer

- Hypercalcemia
 - ⇒ Squamous cell carcinoma is the most common type of cancer related to hypercalcemia.
 - ⇒ Parathyroid hormone-related protein (PTH-rp) secretion causing hypercalcaemia
 - occurs in about 15%
 - best treated with intravenous fluids and bisphosphonates
- Hypertrophic pulmonary osteoarthropathy (HPOA)
 - ⇒ More common with adenocarcinomas than squamous cell carcinomas
 - ⇒ Characterized by abnormal proliferation of the cutaneous and osseous tissues at the distal regions of the extremities.
 - ⇒ a triad of clubbed fingers, symmetric polyarthritis, and periostitis of the long tubular bones
 - ⇒ It is often painful.

Paraneoplastic features associated with small cell lung cancers

- ↑ ADH → Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
 - ⇒ SIADH manifests as euvolemic hypo-osmolar hyponatremia characterized by low serum osmolality and inappropriately high urine osmolality in the absence of diuretic treatment, adrenal insufficiency, heart failure, cirrhosis, or hypothyroidism
- ↑ ACTH → Hypercortisolism → Cushing syndrome
 - ⇒ not typical presentation
 - ⇒ hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness are more common than buffalo hump etc.
 - ⇒ May manifest by Cushingoid facies and hyperpigmentation of the skin

Lambert-Eaton syndrome

- ⇒ 70% occur in small cell carcinoma
- ⇒ is a pre-synaptic disorder of auto-antibody IgG directed against the pre-synaptic voltage gated calcium channel (VGCC) leading to impaired acetylcholine release.
- ⇒ characterised by:
 - Proximal muscle weakness (the cranial nerves and respiratory muscles are usually spared)
 - Depressed or absent tendon reflexes and
 - Autonomic features (for example, dry mouth, impotence, etc).
- ⇒ Weakness and fatiguability can be improved with guanidine hydrochloride
- ⇒ Unlike myasthenia gravis exercise is associated with increasing muscle strength and there is a negative response to Tensilon.

The presence of hyponatraemia strongly points towards a diagnosis of small cell lung cancer.

Lung cancer: stepwise investigations

Chest x-ray

- ⇒ The best choice for an initial study.
- ⇒ No initial examination is complete without a lateral film.
- ⇒ Normal X-ray of the chest does not exclude bronchial carcinoma
- ⇒ The common appearance of a tumour arising from the main central airways (70% of all cases) is enlargement of one or other hilum.
- An endobronchial lesion commonly leads to partial or complete atelectasis and this is the commonest sign of bronchogenic carcinoma.
- ⇒ Consolidation and collapse distal to the tumour might have occurred
- ⇒ Collapse of the left lower lobe is often hard to identify, as is a tumour situated behind the heart.
- ⇒ Apically located masses or superior sulcus tumours (Pancoast tumours) can be misdiagnosed as pleural caps, and patients often have a long history of pain in the distribution of the brachial nerve roots.
- ⇒ The mediastinum might be widened by enlarged nodes.

Contrast-enhanced CT of the lower neck, chest, and upper abdomen

⇒ Perform contrast-enhanced CT of the chest, liver adrenals and lower neck before any biopsy procedure.

⇒ Shows size, location and extent of primary tumour; evaluates for hilar and/or mediastinal lymphadenopathy and distant metastases

Biopsy

- ⇒ If the CT demonstrates a peripheral lung lesion, CT or ultrasound-guided transthoracic needle biopsy should be offered.
- ⇒ Endobronchial ultrasound (EBUS) guided biopsy is recommended for paratracheal and peri-bronchial intra-parenchymal lung lesions.
- Wherever possible minimally invasive procedures should be undertaken first for mediastinal node sampling (e.g., EBUS) before embarking into more invasive procedures like VATS.

Positron-emission tomography (PET)

- ⇒ The preferred first test after CT for intrathoracic lymph node assessment
- PET would determine whether there are distant metastases and is performed after the CT.
- ⇒ For example in a patient with operable non-small-cell lung cancer, if CT has shown enlarged mediastinal nodes, he needs further assessment of his mediastinal nodes prior to surgery, because CT is not particularly good for assessing whether enlarged nodes are inflammatory or malignant. and this can be done with mediastinoscopy or a positron-emission tomography (PET) scan.
- Fluorodeoxyglucose is the usual tracer used for PET imaging in lung cancer
- ⇒ PET is considered a standard staging study for patients with NSCLC; however, pathological confirmation of abnormal findings is often necessary due to false positives.
- ⇒ For patients with known metastatic disease, PET is unnecessary.



Performance status for patient of lung cancer and COPD

- Assessing a patient's performance status is important when evaluating the most appropriate treatment options.
- It is commonly used by cancer MDTs, but has a role in assessing patients with chronic illnesses including COPD.

WHO (Zubrod) Scale	Description
0	Asymptomatic
1	Symptomatic but ambulatory (can carry out light work)
2	In bed less than 50% of the day. Unable to work but can live at home with some assistance
3	In bed more than 50% of the day (unable to care for self)
4	Bedridden

Staging lung carcinoma

Criteria for staging

- TNM staging takes into account:
 - ⇒ The size and position of the tumour (**T**)
 - ⇒ Whether the cancer cells have spread into the lymph nodes (N)
 - ⇒ Whether the tumour has spread anywhere else in the body secondary cancer or metastases (M)
- CT scan is recommended as a staging procedure.
- Where available, PET scanning may be superior.

Chest CT is the best method for staging squamous-cell carcinoma of the lung.

The Tumor, Node, Metastasis (TNM) staging system

 The International Association for the Study of Lung Cancer (IASLC) developed a eighth edition of the TNM system in 2018 replaced earlier editions: as fellow

T, N, and M descriptors for the eighth edition of TNM classification for lung cancer

- T: Primary tumor
 - ⇒ Tx → Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
 - \Rightarrow **T0** \rightarrow No evidence of primary tumor
 - ⇒ **Tis** → Carcinoma in situ

- ⇒ **T1** →Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
 - T1a(mi) → Minimally invasive adenocarcinoma
 - T1a →Tumor ≤1 cm in greatest dimension
 - T1b → Tumor >1 cm but ≤2 cm in greatest dimension
 - T1c →Tumor >2 cm but ≤3 cm in greatest dimension
- ⇒ **T2** → Tumor >3 cm but ≤5 cm or tumor with any of the following features:
 - Involves main bronchus regardless of distance from the carina but without involvement of the carina
 - 2) Invades visceral pleura
 - 3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
 - T2a → Tumor >3 cm but ≤4 cm in greatest dimension
 - **T2b** →Tumor >4 cm but ≤5 cm in greatest dimension
- ⇒ T3 → Tumor >5 cm but ≤7 cm in greatest dimension or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
- ⇒ **T4** → Tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina

N: Regional lymph node involvement

- ⇒ Nx → Regional lymph nodes cannot be assessed
- ⇒ N0 →No regional lymph node metastasis
- ⇒ N1→ Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- ⇒ N2 → Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- ⇒ N3 → Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

. M: Distant metastasis

- ⇒ M0 →No distant metastasis
- ⇒ M1 →Distant metastasis present
 - M1a →Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion◊
 - M1b → Single extrathoracic metastasis§
 - M1c → Multiple extrathoracic metastases in one or more organs

Treatment of lung cancer (NICE guidelines 2019)

Non-small-cell lung cancer (NSCLC)

Surgery

- ⇒ for early-stage NSCLC I–IIA (T1a–T2b, N0, M0) → lobectomy
- ⇒ Advise to stop smoking, offer nicotine replacement therapy, but do not postpone surgery for that.
- ⇒ Assessment before surgery for NSCLC
 - assess perioperative mortality by using risk scores such as thoracoscore.
 - Avoid surgery within 30 days of myocardial infarction.
 - Consider revascularisation (percutaneous intervention or coronary artery bypass grafting) before surgery for people with chronic stable angina
 - Perform spirometry and transfer factor (TLCO)

Radical radiotherapy

- ⇒ For people with stage I–IIA (T1a–T2b, N0, M0) NSCLC who decline surgery or in whom any surgery is contraindicated, offer radical radiotherapy with stereotactic ablative radiotherapy (SABR). If SABR is contraindicated, offer either conventional or hyperfractionated radiotherapy.
- ⇒ For eligible people with stage IIIA IIIB NSCLC who cannot tolerate or who decline chemoradiotherapy, consider radical radiotherapy (either conventional or hyperfractionated).

Combination treatment (chemoradiotherapy)

- ⇒ For people with stage II or III NSCLC that are not suitable for or decline surgery.
- ⇒ For people with operable stage IIIA–N2 NSCLC: consider chemoradiotherapy with surgery.

Systemic anti-cancer therapy (SACT) for advanced NSCLC

- ⇒ For non-squamous non-small-cell lung cancer, stages IIIB and IV
 - If the tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation → Afatinib
 - If the tumour tests positive for anaplastic lymphoma kinase (ALK) gene → Crizotinib or Alectinib
 - If the tumour tests positive for PD-L1 above 50% → Pembrolizumab

- If the tumour tests positive for PD-L1 below 50% → gemcitabine or vinorelbine and cisplatin or carboplatin
- If the tumour tests positive for **ROS1**→ Crizotinib

Contraindications to lung cancer surgery include SVC obstruction, FEV < 1.5, MALIGNANT pleural effusion, and vocal cord paralysis

Treatment of non-small cell lung cancer (NSCLC)

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NSCLC stage	Treatment	
Stage I (cT1N0 and cT2N0) (primary tumour <5	Surgery	
cm) and stage II (primary tumour >5 cm, or	(FEV-1 should be >1.5 litres & no	
smaller primary tumour with metastasis to a nearby	mets)	
lymph node) (cT1N1, cT2N1 and cT3N0)		
stage III (ipsilateral lung metastases or multiple	Sequential chemo-radiotherapy	
metastases to nearby lymph nodes):		
Stage IV (metastatic)	chemotherapy alone	

- Absolute contraindications for surgery include:
 - ⇒ FEV1 < 1.5 litres is considered a general cut-off point
 - If the tumour necessitates a pneumonectomy, the post-bronchodilator FEV should be more than 2 litres.
 - ➡ Reduction in the gas transfer test of more than 50% is a contraindication to surgery.
 - ⇒ Metastases.
 - stage IIIb or IV (i.e. metastases present)
 - Tumour near hilum
 - Vocal cord paralysis (implies extracapsular spread to mediastinal L.N)
 - SVC obstruction
 - Malignant pleural effusion (not just 'pleural effusion' (which may be reactive)). Most pleural effusions associated with lung carcinoma are due to the tumour (and results in classification as a T4 tumour).
 - Spread to involve the C8, T1 and T2 nerve roots occurs by rib erosion by tumour to involve the lower roots of the brachial plexus and is known as a Pancoast tumour.

Small-cell lung cancer (SCLC)

- Early-stage SCLC (T1–2a, N0, M0): Consider surgery
- Limited-stage disease SCLC (T1-4, N0-3, M0) → 4 to 6 cycles of cisplatin-based combination chemotherapy + thoracic radiotherapy + prophylactic cranial irradiation
- Extensive-stage disease SCLC (broadly corresponding to T1–4, N0–3, M1a/b including cerebral metastases)
 platinum-based combination chemotherapy up to a maximum of 6 cycles + thoracic radiotherapy with prophylactic cranial irradiation

Treatment of small cell lung cancer (SCLC)

Trouble of Children Con Family Canada (CC20)			
Stage of SCLC	Treatment		
Early stage (T1-2a,N0,M0)	Surgery		
	4-6 cycles cisplatin-based chemotherapy, carboplatin if poor renal function/poor performance status +/- radiotherapy		
Extensive disease (T1-4, N0- 3, M1a/b)	6 cycles platinum-based combination chemotherapy + thoracic radiotherapy if good response		

The most appropriate next step in management for patients with SCLC who have a response to initial chemotherapy → Prophylactic cranial irradiation should be considered

Palliative care

- Impending endobronchial obstruction → external beam radiotherapy and/or endobronchial debulking or stenting
- pleural effusion → pleural aspiration, talc pleurodesis for longer-term benefit.
- to reduce cough → opioids, such as codeine or morphine
- superior vena cava obstruction → chemotherapy and radiotherapy
- for the immediate relief of severe symptoms of superior vena caval obstruction → stent insertion
- $\bullet \quad \text{for symptomatic brain metastases} \to \ \text{dexamethasone}$
- for bone metastasis who need palliation and for whom standard analgesic treatments are inadequate → single-fraction radiotherapy

Lung cancer induced superior vena cava obstruction (SVCO)

Overview

- SVCO an oncological emergency caused by compression of the SVC.
- 60 % of patients present with SVC syndrome without a preexisting diagnosis of cancer.
- Most commonly associated with lung cancer.
 - ⇒ Up to 4% of patients with lung cancer will develop SVCO at some point during their disease.
 - ⇒ SVCO is much more likely to be associated with right sided lung lesion 4 times than with left sided lesions

Causes

- Lung cancer
 - ⇒ Non-small cell lung cancer (the most common cause ≈ 50%)
 - ⇒ Small cell lung cancer (25%)
- Non-Hodgkin lymphoma (NHL) (10%)
- Other malignancies (15%)
 - ⇒ metastatic seminoma, Kaposi's sarcoma, breast cancer
- Aortic aneurysm
- Mediastinal fibrosis
- Mediastinal goitre
- SVC thrombosis

Features

- · Dyspnoea is the most common symptom
- Swelling of the face, neck and arms conjunctival and periorbital oedema may be seen
- Headache
- Visual disturbance
- Pulseless jugular venous distension
- CXR is abnormal in around 85% of cases, mediastinal widening is common.

Association

- Recurrent laryngeal nerve palsy (voice hoarseness): usually occurs with malignant tumour but can occur with aneurysm of aortic arch.
- Horner's syndrome due to involvement of sympathetic chain.
- elevated non-pulsatile jugular venous pressure (JVP)
- Compression of vital structures can result in stridor and dysphagia.

Diagnosis

- Duplex ultrasound
 - ⇒ The initial imaging study for patients with mild symptoms
- Contrast-enhanced CT
 - The initial study for patients with clinical features suggestive of moderate SVC syndrome
- Venography
 - ⇒ The first line in severe or life-threatening symptoms
 - Catheter-based (standard) venography is preferred over CT venography because it also provide immediate treatment by thrombolysis (pharmacologic or mechanical) and SVC stenting

Management

- Dexamethasone
 - Corticosteroids are most useful where the cause of compression is an underlying haematological malignancy.
 - ⇒ SVCO: immediate management → Dexamethasone IV + LMWH.
- Stenting
 - ⇒ Relieves symptoms quicker than chemotherapy or radiotherapy.
- Radiotherapy
 - ⇒ may be an option <u>later</u>. If radiotherapy is used initially then stenting becomes significantly more difficult due to local fibrosis.
 - ⇒ Mediastinal radiotherapy leads to symptomatic relief in 80% of patients

Pancoast tumor

- An apical lung carcinoma
- Located in the superior sulcus of the lung (superior sulcus tumor)
- Predominantly non-small cell lung cancer (NSCLC)
- May lead to the development of Pancoast syndrome: a group of symptoms secondary to the mass effect of the tumor on surrounding structures
 - ⇒ Cervical sympathetic ganglion (stellate ganglion): → Horner syndrome (ipsilateral miosis, ptosis, and anhidrosis)

- ⇒ Recurrent laryngeal nerve: → hoarseness
- ⇒ Phrenic nerve: → paralysis of the hemidiaphragm (visible as elevated hemidiaphragm on chest x-ray)
- ⇒ **Brachial plexus**:→ shoulder pain, sensorimotor deficits (eg, atrophy of intrinsic muscles of the hand)
- ⇒ Brachiocephalic vein: → unilateral edema of the arm and facial swelling
- The investigation of choice → CT of chest
- Treatment: usually inoperable on presentation → radiation and chemotherapy

Lung metastases

Metastatic carcinoma is the most common malignant tumour found in the lung

- Metastatic carcinoma is the most common malignant tumour found in the lung
- Malignant metastases to the lung can present as a solitary enlarging nodule, as multiple nodules or with diffuse lymphatic involvement.
- The most common causes of malignant nodules are primary lung cancer, lung metastases, and carcinoid tumors.
- Breast, Colorectal, renal and lung primaries are the commonest underlying tumours.
- An incidental pulmonary nodule that has clearly grown on serial imaging or is 18fluorodeoxyglucose (FDG)-avid on positron emission tomography (PET)/CT is likely to be malignant and should be evaluated with biopsy.
- A diagnosis can usually be secured by percutaneous computed tomography- (CT-) guided biopsy.

Lung cancer with multiple brain metastases → Hospice care is appropriate.



Metastatic carcinoma

Chest X-ray shows secondary tumors as multiple, well-circumscribed, noncalcified nodules.

The most common cancer to present with metastases to the hand is lung cancer.

Carcinoid lung tumour

Carcinoid tumour as general (see gastroenterology section)

- neuroendocrine tumours of predominantly enterochromaffin cell origin.
- can occur in the small intestine, bronchi, rectum appendix or stomach.

Overview

- The vast majority of bronchial adenomas are carcinoid tumours, arising from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours.
- Carcinoid tumours (so called argentafinomas as they take up silver) are neuroendocrine cells
- originate from Kulchitsky (K) cells in the lung
- Most often located in the main bronchi, and occur most frequency in the right middle lobe.
- slow growing
- smoking is NOT a risk factor

Epidemiology

- 1% of lung tumours
- 10% of carcinoid tumours.
- typical age = 40-50 years
- The incidence is equal between men and women.

Feature

Recurrent haemoptysis with segmental collapse on x-ray is a typical presentation of bronchial carcinoid.

- Often asymptomatic
- long history of cough, recurrent haemoptysis
- Recurrent infections: carcinoid tumours → (80-90%) develops in a bronchus → bronchial obstruction → lower respiratory tract infection.
- Carcinoid syndrome (rare)
 - ⇒ depends on associated liver metastases
 - ⇒ occurs in less than 10% of patients with carcinoid tumours, but occurs most commonly in GIT tumours.
 - can secrete a number of vasoactive compounds (including serotonin and bradykinin), which result in bronchospasm, diarrhoea, skin flushing and rightsided valvular heart lesions.
- ⇒ Paraneoplastic syndromes
 - ACTH secretion and subsequent Cushing's syndrome.
 - Ectopic growth hormone-releasing hormone [GHRH] and subsequent acromegaly
 - Multiple endocrine neoplasia (MEN) type 1 where pancreatic neuroendocrine tumours predominate.

Investigations

The 'cherry-red' lesion is a typical finding of lung carcinoid.

- Chest-X ray
 - ⇒ often **centrally** located and not seen on CXR.
 - ⇒ A carcinoid tumour in the left lower lobe bronchus could cause distal collapse of the left lower lobe.
- · Bronchoscopy:
 - ⇒ Identifies up to 80% of carcinoid tumours in the main bronchi.
 - ⇒ seen as a highly vascular 'cherry-like' tumour ('cherry red ball')
 - ⇒ Biopsy is usually followed with brisk bleeding and should be done via rigid bronchoscopy.
 - ⇒ The histological picture of granular eosinophilic staining of the cytoplasm, is highly suggestive of a carcinoid tumour.
 - ⇒ Histologically, these tumors consist of compact nests of epithelial cells surrounded by neat, delicate connective tissue capsules.
 - histology might not be necessary prior to surgery if the clinical picture is typical.
- Plasma chromograffin A is an effective screening test for carcinoid as it is very sensitive, but it is not specific.
- **24-hour urinary excretion of 5-hydroxyindoleacetic acid** is **more specific** for the **diagnosis**, but false positives and negatives are present.

Management

- Surgical resection
 - A person with an isolated pulmonary carcinoid should be referred for tumour resection,
 - ⇒ histology might not be necessary prior to surgery if the clinical picture is typical.

Prognosis

if no metastases then 90% survival at 5 years

Lung fibrosis: Causes

Acronym for causes of upper zone fibrosis: CHARTS

- C- Coal worker's pneumoconiosis
- H Histiocytosis/ hypersensitivity pneumonitis
- A Ankylosing spondylitis
- R Radiation
- T Tuberculosis
- S Silicosis/sarcoidosis

Fibrosis predominately affecting the upper zones

- Extrinsic allergic alveolitis
- Coal worker's pneumoconiosis/progressive massive fibrosis
- Silicosis (Silica is found in coal dust)
- Sarcoidosis
- Ankylosing spondylitis (rare)
- Histiocytosis: Pentalaminar X bodies (Birbeck granules) found on bronchoalveolar lavage (BAL) are diagnostic.
- Tuberculosis
- Allergic bronchopulmonary aspergillosis and farmers lung
- Radiation

Fibrosis predominately affecting the lower zones

- Idiopathic pulmonary fibrosis (IPF) (previously known as Cryptogenic fibrosing alveolitis (the more common cause)
- Most connective tissue disorders (except ankylosing spondylitis)
- Asbestosis
- Drug-induced
 - ⇒ Cardiac drugs: **amiodarone**, hydralazine
 - ⇒ Cytotoxic agents: busulphan, **bleomycin** , cyclophosphamide, leflunomide
 - ⇒ Anti-rheumatoid drugs: methotrexate, sulfasalazine, gold
 - ⇒ Antibiotics: nitrofurantoin
 - ⇒ Ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide).
 - ⇒ Opiates: e.g. heroin abuse

Baseline pulmonary function testing is important in patients receiving bleomycin

Pulmonary fibrosis can occur following pneumonia

Idiopathic pulmonary fibrosis (IPF)

Definition

Progressive fibrosis of the interstitium of the lungs when no underlying cause exists.

Epidemiology

- Most common type of interstitial lung disease (ILD)
- Typically seen in patients aged 50-70 years
- Men are affected more than women

Pathophysiology

Recurrent microinjuries to the alveolar wall → ↑growth factors secreted by the injured epithelial cells (most commonly: Transforming growth factor-beta (TGF-beta) → recruit fibroblasts → differentiate into myofibroblasts → secrete interstitial collagen, which accumulates due to imbalance between interstitial collagenases and their tissue inhibitors.

Risk factors

- · Genetic predisposition,
- · Cigarette smoking, environmental pollutants
- Chronic microaspiration.

Features

- Gradual onset (over several months) of exertional dyspnoea and dry cough
- Bibasal crackles on auscultation
- · Clubbing occurs in two-thirds of cases.

Diagnosis

- Chest X-ray: Bilateral Iower-zone reticulonodular shadows
- High resolution computed tomography (HRCT)
 - ⇒ The investigation of choice
 - ⇒ Showa radiographic pattern of usual interstitial pneumonia (UIP):
 - 1. Peripheral (subpleural), bibasilar reticular opacities
 - Architectural distortion, including honeycomb changes and traction bronchiectasis or bronchiolectasis
- Spirometry → restrictive picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased)
- Transfer factor (TLCO) reduced, most useful in determining prognosis.
- Lung biopsy by video-assisted thoracoscopy (VATS)
 - ⇒ If HRCT is not diagnostic
 - ⇒ Finding → Honeycombing and collagen deposition with fibroblast foci
- Exclusion of other known causes of interstitial lung disease

Usual interstitial pneumonia (UIP): is a radiologic and pathologic description and can be seen in conditions other than IPF, especially connective tissue diseases, rheumatoid arthritis. Once these other conditions are reasonably excluded, a clinical diagnosis of IPF can be made. Hence UIP does not always mean IPF. But in IPF, the radiologic and pathologic pattern is UIP.

Management

- Supportive care (eg, supplemental oxygen, pulmonary rehabilitation, seasonal influenza and pneumococcal vaccination)
- Antifibrotic agents → pirfenidone or nintedanib
 - ⇒ Action → suppresses fibroblast proliferation
 - ⇒ Indication → mild-moderate disease IPF (FVC 50-80 % predicted).
 - ⇒ Benefit → reduces disease progression by 30 %
 - ⇒ Side effects → drug-induced liver injury
- Immunosuppressant therapies such as azathioprine, prednisolone and mycophenolate mofetil should not be used in IPF.
- Lung transplant

Prognosis

- poor, average life expectancy is around 3-4 years
- increased risk of developing lung cancer (by 7- to 14-fold).



Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs



CT scan showing advanced pulmonary fibrosis including 'honeycombing'

Bronchiolitis obliterans (BO)

Definition

 'Bronchiolitis obliterans' is the term used to describe fibrous scarring of the small airways, characterized by fixed airway obstruction.

Mechanism

- submucosal and peribronchiolar inflammation and fibrosis without any intraluminal granulation tissue
- BO should not be confused with bronchiolitis obliterans organising pneumonia (BOOP), a completely different disease.

Causes

- · Inhalation of toxic fumes
- Exposure to mineral dust
- Respiratory infections: Viral, Mycoplasma, Legionella
- post-transplantation: Bone marrow, heart-lung or lung transplantation
- Connective tissue disorder: Rheumatoid arthritis or SLE
- Penicillamine treatment
- · inflammatory bowel disease

Feature

- · dry cough and dyspnoea.
- wheeze might be audible.

Diagnosis

- Should be considered in a nonsmoker when airflow limitation is irreversible or associated with a gas transfer abnormality.
- Should be considered in association with recent toxic fume exposure, symptoms of viral infection, history of organ transplantation, or concomitant rheumatic disease.
- HRCT: shows expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules
- Spirometry → mixed obstructive/restrictive picture
- Transfer factor may be low but the transfer coefficient (Kco) is often normal.
- lung biopsy
 - ⇒ An open or thoracoscopic lung biopsy is required to make a definitive diagnosis
 - ⇒ will show→ a mural concentric narrowing of the lumina of the bronchioles.
 - ⇒ Transbronchial lung biopsy is often inadequate for diagnosis because the disease is patchy.

Differential Diagnosis

- Bronchiolitis obliterans is often misdiagnosed as asthma, chronic bronchitis, emphysema or pneumonia.
 - ⇒ Asthma → reversible airflow limitation on spirometry (unlike BO)
 - ⇒ COPD → significant cigarette smoking history and no exposure to the etiologic agents for BO.
 - ⇒ Cryptogenic organising pneumonia (COP) : differ from BO in:
 - 'cryptogenic means unknown cause'.
 - granulation tissue in the alveoli and bronchioles on histopathology
 - Spirometry → restrictive pattern
 - Responds very well to steroids

Treatment

- No optimal treatment. Patients rarely respond to steroids and the prognosis is poor.
- This disease is irreversible and severe cases often require a lung transplant

a history of inhalational exposure or hematopoietic cell or lung transplantation, the combination of airflow limitation on spirometry and HRCT showing expiratory air trapping (mosaic or diffuse), bronchial wall thickening, and centrilobular nodules are sufficient to make a diagnosis of bronchiolitis obliterans.

Post-extubation stridor (PES)

Prevalence

PES is a frequent complication of intubation, occurring in 2-16% of cases.

Pathophysiology

 pressure and ischaemia → damage to the mucosa of the larynx → inflammatory response → laryngeal oedema → acute respiratory compromise necessitating emergency reintubation.

Risk factors for post-extubation stridor from laryngeal edema

- prolonged duration of intubation,
- traumatic intubation, (variably defined as ≥36 hours to ≥6 days)
- large tube size (>8 mm in men, >7 mm in women)
- · Excessive cuff pressure
- Aspiration
- Tracheal infection
- · A history of asthma
- Female gender

Obstantilla de la companya (OOA)

Obstructive sleep apnoea (OSA)

Sleep apnoea causes include obesity and macroglossia

Definition

 Cessation of breathing during sleep because of upper airway obstruction leads to apnea (respiratory arrests of ≥ 10 seconds) and hypopnea (reduction of airflow by ≥ 50% for ≥ 10 seconds).

Epidemiology

• More common in men : 3 > 2 (2:1)

Causes

- Obesity: the most important risk factor
- macroglossia: acromegaly, hypothyroidism, amyloidosis
- large tonsils
- Marfan's syndrome
- · Small pharyngeal opening
- Coexisting COPD
- Sedatives such as alcohol
- Collar size (Neck size) greater than (17 inches) 43 cm is strongly associated.

Features

- Excessive daytime somnolence as a result of repeated arousals.
- Repetitive apnoeas (cessation of airflow for more than 10 seconds) and hypopnoeas (50% reduction in airflow for greater than 10 seconds)
- · loud snoring, gasping, choking or interruptions in breathing while sleeping
- · morning headaches

Complications

- Pulmonary hypertension and cor pulmonale
- Hypoxia-induced cardiac arrhythmia
- increased risk of premature death, sudden death
- myocardial infarction, stroke,
- motor vehicle accidents due to microsleep
- metabolic syndrome (hypertension, insulin resistance → ↑ risk of type 2 diabetes.)
- · neurocognitive dysfunction, vascular dementia
- · reduced libido and erectile dysfunction
- CBC may show polycythemia (↑ Hct, ↑ Hb): Hypoxia induces erythropoietin secretion by the kidneys, which stimulates the blood marrow, leading to increased RBC production

Obstructive sleep apnea is one of the most common causes of secondary hypertension.

Diagnosis: Sleep studies

- Overnight polysomnography: first-line method
 - ⇒ The gold standard diagnostic test is.
 - ⇒ Classic findings
 - ⇒ Diagnose **OSA** if the **Apnoea-Hypopnoea Index (AHI)**:
 - ≥15 episodes/hour.
 - ≥ 5 episodes/hour + additional symptoms (eg: excessive daytime sleepiness, insomnia, mood disorder, or cognitive dysfunction) or comorbidities (eg: HTN, IHD, stroke)
 - ⇒ To assess severity of obstructive sleep apnoea → Apnoea-Hypopnoea Index (AHI):
 - mild → 4-14 episodes
 - moderate → 15-30 episodes
 - severe → >30 episodes

The diagnosis of obstructive sleep apnea requires sleep studies and should not be made based on clinical tools or questionnaires alone such as Epworth Sleepiness Scale (used to diagnose excessive daytime sleepiness) or Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

In-laboratory polysomnography is the gold standard for the diagnosis of sleeprelated breathing disorders

Following weight loss, CPAP is the first-line treatment for moderate/severe obstructive sleep apnoea

Management

- Weight loss. the definitive management. But takes time
- Continuous positive airways pressure ventilation (CPAP): the treatment of choice
 - ⇒ the most appropriate <u>initial</u> and quickest management
- Intra-oral devices (e.g. **Oral appliance**, mandibular advancement)
 - ⇒ if CPAP is not tolerated or for patients with mild OSA where there is no daytime sleepiness
- Upper airway surgery: if CPAP or an oral appliance are declined or ineffective.
- Pharmacological agents: limited evidence
 - ➡ Modafinil is a drug that is licensed for excessive daytime sleepiness in people with OSA treated with CPAP, as well as for narcolepsy.
- Avoid sedatives drugs/excess alcohol

Obesity hypoventilation syndrome (OHS) (Pickwick syndrome)

Obesity + feature of OSA + diurnal abnormal ABG (↑ PCO2) → (OHS)

Definition

 a combination of obesity (body mass index [BMI] ≥30 kg/m²) and daytime hypercapnia (PaCO₂ ≥45 mm Hg in arterial blood gas analysis) in the absence of other causes for hypoventilation.

Diagnostic criteria

- BMI ≥ 30 kg/m². Commonly affects morbidly obese individuals. 90% of patients with OHS have coexistent OSA.
- Arterial blood gasses showing diurnal hypercapnia (PaCO₂ > 45 mm Hg)
 - ⇒ serum bicarbonate ≥ 27 mEg/L
- Polysomnography: hypoventilation during sleep with or without obstructive apnea events
- Exclusion of other possible causes of hypoventilation (eg, neuromuscular disease).

Treatment

 1st line: noninvasive positive airway pressure (PAP) together with lifestyle modifications for weight loss.

Pneumothorax

Classification

- primary pneumothorax : if there is no underlying lung disease.
- **secondary** pneumothorax : if there is underlying lung disease

Features

- Sudden onset of chest pain, sometimes radiating to the shoulder
- Dyspnoea (may not be a dominant feature)
- · Dry cough

 Hamman's sign (or 'crunch') is a clicking sound synchronous with the heart-beat, heard over the sternal edge in mediastinal emphysema or Left-sided pneumothoraces.

Risk factors

- Young adult males, <u>often tall and slim</u>, are frequently affected by <u>spontaneous</u> <u>pneumothorax</u>.
- Patients with **Marfan** syndrome are prone to **recurrent pneumothoraces**.

Investigations

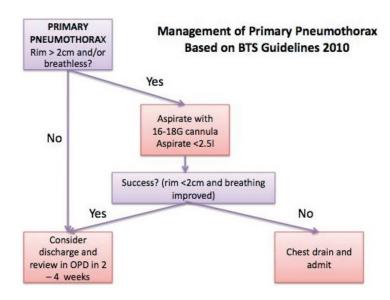
- Chest x ray: 1st step to confirm the diagnosis
 - ⇒ Questions sometimes discuss the size of the pneumothorax in percentage terms rather than giving the interpleural distance.
 - ⇒ A 30% pneumothorax ≈ 2 cm
 - \Rightarrow A 50% pneumothorax is likely to have a rim of > 3cm.
- CT chest
 - ⇒ The next step after chest x-ray to investigate the underlying cause of recurrent pneumothorax
- Video assisted thoracoscopy
 - ⇒ If CT not help in pointing to underlying cause of recurrent pneumothorax

Differential diagnosis

- Large bullae in COPD can mimic a pneumothorax:
 - the most appropriate management option → CT chest to confirm
 - place a needle or chest drain would be disastrous → shrinkage of the lung

Management

- Primary pneumothorax
 - ⇒ **Definition:** Spontaneous primary pneumothorax is defined as:
 - Age less than 50-years-old
 - No <u>significant</u> smoking history, minimal smoking history would still be considered as primary pneumothorax
 - No evidence of underlying lung disease.
 - **⇒** Caused by the rupture of apical pleural blebs.
 - ⇒ Management
 - If the rim of air is < 2cm and the patient is not short of breath then discharge should be considered
 - If the rim of air is ≥ 2cm or the patient is breathless → Needle aspiration
 - If following aspiration the rim of air is < 2cm and the breathing has improved then discharge should be considered with outpatient review.
 - If needle aspiration fails (defined as > 2 cm or still short of breath) → chest drain should be inserted
 - If a patient with a pneumothorax requires oxygen, this should be given at 10 L/min.



Secondary pneumothorax

- ⇒ Definition: the patient is ≥ 50 years old, or has <u>significant</u> smoking history or evidence of underlying lung disease.
- ⇒ Management:
 - If the rim of air is < 2cm → aspiration</p>
 - If the rim of air is ≥ 2cm → chest drain → Insert a small-bore chest drain (8-14 FG) and attach to an underwater seal drain
 - If aspiration fails (i.e. pneumothorax is still >1cm) → a chest drain should be inserted.
 - if the patient is very dyspneoic a drain should be inserted even though the pneumothorax is small (< 2cm).
 - All patients should be admitted for at least 24 hours
 - High flow oxygen should be given in all cases of pneumothorax, as it facilitates re-absorption of the pleural air, which is predominantly composed of nitrogen.

Asthmatics should be treated as a secondary pneumothorax

Tension pneumothorax

- should be suspected in people on mechanical ventilators or nasal non-invasive ventilation who suddenly deteriorate, and is frequently missed in the intensive care unit setting.
- Treatment → needle thoracocentesis
 - ⇒ use a 3-6-cm-long cannula to perform needle thoracocentesis.
 - ⇒ the cannula should be left in place until bubbling is confirmed in the underwaterseal system to confirm proper function of the intercostal tube.

If the history and examination are suggestive of a pneumothorax and the patient being relatively stable (tension pneumothorax are not suggested), the most appropriate first step would be \rightarrow confirmation with chest x ray rather than place a needle or chest drain.

Chest drains for pneumothorax

- Point of insertion → in the 'safe triangle', in the mid-axillary line, above a rib margin
- · Chest drain situations
 - ⇒ When the patient coughs, nothing happens. When he breathes in and out, the fluid in the tube moves up and down that means → Air is no longer draining from the pleural space, but the drain is still working. Air is not bubbling out of the drain when the patient coughs because the air has stopped draining from the pleural space and the lung has re-inflated.
 - ⇒ If a drain does not bubble or swing, then it is blocked or kinked and is not working.
- Next step after failure of chest drain
 - ⇒ Negative suction is necessary if the drain is still bubbling but the lung has not fully re-inflated on the chest X-ray. After chest drain if pneumothorax fails to re-expand or if there is a persistent air leak (bubbling present) after 48 hours, then you should → refer the patient to a respiratory specialist because negative suction might be required using a high-volume/low-pressure suction system.
 - ⇒ Cardiothoracic surgical referral → Video assisted thoracoscopic surgery indications:
 - persistent pneumothorax despite low-pressure, large-volume suction, and the chest drain in position and is bubbling (may be have a bronchopleural fistula)
 - Persistent air leak (more than five to seven days of drainage)
 - Second ipsilateral pneumothorax for bullectomy and pleurectomy.
 - Bilateral spontaneous pneumothorax
 - Certain occupations, for example, pilots or divers.
 - ⇒ **Chemical pleurodesis** through the chest drain:
 - used in <u>older</u> patients or frail individuals with <u>recurrent</u> pneumothorax, where surgery would be high risk.

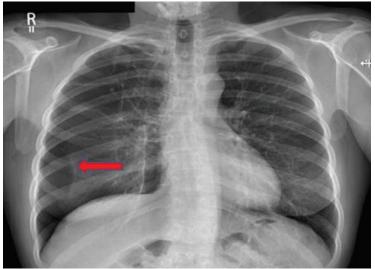
Fitness to fly

- Pneumothorax is an absolute contraindication to air travel as trapped air may expand and result in a tension pneumothorax.
- In general, it should be safe to travel approximately 1- 2 weeks after successful drainage of a pneumothorax with full expansion of the lung.

Divina

 The British Thoracic Society (BTS) guidelines state: 'Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively.'

Images



Chest x ray reveals a 3.2 cm rim of air around the lung.

Pleural effusion

Classification, pathophysiology and causes

	Exudate (> 30g/L protein)	Transudate (< 30g/L protein)	
Pathophysiology	↑ Capillary hydrostatic pressure (increased capillary wedge pressure) ↓ Capillary oncotic pressure	↑ Capillary permeability (e.g., due to inflammation)	
Causes	 infection: pneumonia, TB, sub-phrenic abscess connective tissue disease: RA, SLE neoplasia: lung cancer, mesothelioma, metastases pancreatitis pulmonary embolism Dressler's syndrome yellow nail syndrome 	 heart failure hypoalbuminaemia ⇒ liver disease, ⇒ nephrotic syndrome, ⇒ malabsorption hypothyroidism Meigs' syndrome 	

Investigation

- Chest x-rays should be performed in all patients
- Ultrasound thorax:
 - ⇒ the next most appropriate step after chest x-ray
 - ⇒ Ultrasound is better for pleural imaging than CT.
 - ⇒ it increases the likelihood of successful pleural aspiration and is sensitive for detecting pleural fluid septations
- Pleural aspiration
 - ⇒ ultrasound is recommended to reduce the complication rate
 - ⇒ a 21G needle and 50ml syringe should be used
 - ⇒ fluid should be sent for pH, protein, lactate dehydrogenase (LDH), cytology and microbiology
- Thoracoscopy
 - the investigation of choice in patients with cytology negative exudative effusions.
- Video-assisted thoracoscopic surgery (VATS)
 - ⇒ A minimally invasive procedure, used if the diagnosis remains unclear

Light's criteria

- Developed to distinguish between a transudate and an exudate.
- The BTS recommend using the criteria for borderline cases:
 - ⇒ exudates have a protein level of >30 g/L, transudates have a protein level of <30 g/L</p>
 - ⇒ if the protein level is between 25-35 g/L, Light's criteria should be applied.

	Exudates	Transudate
Pleural fluid protein/serum protein ratio	> 0.5	≤ 0.5
Pleural fluid LDH/serum LDH ratio	> 0.6	≤ 0.6
Pleural fluid LDH		< ⅔ the upper limit of normal serum LDH

To differentiate exudates from transudates, remember that Exudates have Extra (think protein, LDH).

Pleural infection

- All patients with a pleural effusion in association with sepsis or a pneumonic illness require **diagnostic pleural fluid sampling**
- Indications for chest tube insertion in patients with an infected pleural effusion are:
 - ⇒ Frankly purulent pleural fluid
 - ⇒ Pleural pH < 7.2 in the setting of an infected pleural effusion
 - ⇒ Presence of organisms on a Gram stain of the pleural fluid
 - ⇒ Loculated pleural effusions
 - ⇒ Poor clinical progress despite antibiotic treatment

- What test can be performed to assess if the effusion is an empyema?
 - ⇒ Centrifugation of the pleural aspirate
 - If the pleural fluid is turbid or milky it should be centrifuged. If the supernatant (liquid which lies above the sediment) is clear, the turbid fluid was due to cell debris and empyema is likely

Characteristic pleural fluid findings

- Low glucose
 - **⇒** Empyema
 - ⇒ Rheumatoid arthritis effusions (↓glucose, ↓pH < 7.2, ↑ LDH, ↑ cholesterol, ↑RF)
 </p>
 - ⇒ Tuberculosis
 - ⇒ Malignancy
 - ⇒ Oesophageal rupture
 - ⇒ Lupus
- · Raised amylase
 - ⇒ Pancreatitis.
 - ⇒ Oesophageal perforation
- Heavy blood-staining
 - ⇒ Mesothelioma, malignancy.
 - ⇒ Pulmonary embolism
 - ⇒ Tuberculosis

Complications of plural fluid drainage

- Re-expansion pulmonary oedema
 - ⇒ This is a potentially life-threatening condition which can occur when a large volume of fluid or air is rapidly drained,
 - ⇒ It is suggested by sudden onset of shortness of breath, cough and hypoxaemia following chest drain insertion.

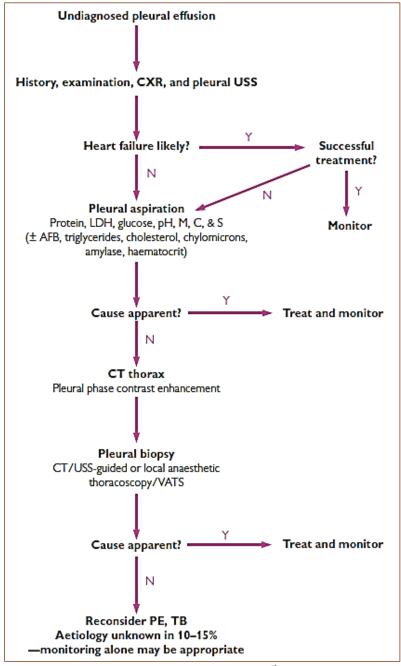
Exudate typically appears cloudy, has an increased cell count, and has high levels of protein, albumin, and LDH.

Transudate is usually clear, has a decreased cell count, and has low levels of protein, albumin, and LDH.

MEAT has low glucose: **M**alignancy, **E**mpyema, **A**rthritis (rheumatoid pleurisy), and **T**uberculosis are causes of pulmonary effusion associated with low glucose levels.

Pleural fluid with a bloody appearance suggests a malignant etiology or haemothorax

Diagnostic algorithm for the patient with a pleural effusion



Oxford handbook of respiratory medicine. 3rd edition

MRCPUK-part-2-march-2018: A patient admitted with severe pneumonia and pleural effusion, despite treatment with Tazocin[®]. Needle aspiration of 15 ml of pleural fluid reveals it to be pus-coloured, with a pH of 7.1 and a glucose level of 3.1 mmol/l. what is the most important intervention?

⇒ Chest drain insertion

Meigs syndrome: A triad of ascites, right pleural effusion, and benign ovarian tumor

Chylothorax

Definition

- Accumulation of chyle (a fatty lymphatic fluid with milky appearance) in the pleural space.
- Chyle is a lymphatic fluid with a high content of triglycerides in the form of chylomicrons, which produce the milky appearance.

Causes

- Nontraumatic chylothorax : Malignancy (classically lymphoma) is the leading cause.
- Traumatic chylothorax: surgical injury to the thoracic duct is the most common cause

Features

• Symptoms induced by the mechanical effects of a pleural effusion

Diagnosis

- Pleural fluid
 - ⇒ for triglyceride and cholesterol levels:
 - elevated triglyceride strongly supports the diagnosis.
 - Low cholesterol will differentiate chylothorax from cholesterol pleural effusion (Pseudochyle → low triglyceride , high cholesterol and empyema)
 - ⇒ Milky appearance is a classic sign of chylothorax
 - ⇒ Pleural fluid is classically exudative with a high lymphocyte count (>70 %), a normal glucose level, a low LDH, and a low cholesterol level).
 - Detection of chylomicrons by lipoprotein electrophoresis is the definitive diagnostic test but not routinely performed

Haemothorax

Definition

· Bleeding into the pleural space

Causes of nontraumatic haemothorax

- Most common: spontaneous pneumothorax
- Less common
 - ⇒ Vascular disease
 - ⇒ Malignancy

- ⇒ Coagulation disorders
- ⇒ Necrotizing pneumonia

Diagnosis

- Pleural fluid analysis
 - ⇒ Bloody appearance
 - ⇒ RBC count > 5.000 cells/ml
 - ⇒ haematocrit that is more than half that of peripheral blood. (Haematocrit > 0.5 × peripheral hematocrit). This distinguishes it from a blood-stained effusion.

Management

The treatment of choice is to insert a large intercostal drain (28-32 F). If this reveals
continued bleeding, a thoracotomy might be required.

A hemothorax, however small, must always be drained because blood in the pleural cavity will clot if not evacuated, resulting in a trapped lung or an empyema.

Eosinophilic Pulmonary Diseases

Definition

• Eosinophilic pulmonary diseases are a heterogeneous group of disorders characterized by the accumulation of eosinophils in alveolar spaces, the interstitium, or both.

Causes of pulmonary eosinophilia

- Known etiology
 - ⇒ Allergic bronchopulmonary aspergillosis (ABPA)
 - ⇒ Helminth infections
 - ⇒ Drug-induced pneumonitis (eg. antibiotics, phenytoin, or L-tryptophan)
 - ⇒ Eosinophilic granulomatosis with polyangiitis (previously referred to as Churg-Strauss syndrome)
 - ⇒ Loffler's syndrome
 - ⇒ Tropical pulmonary eosinophilia
- Unknown etiology: The two primary eosinophilic pulmonary diseases of unknown etiology are
 - ⇒ Acute eosinophilic pneumonia
 - ⇒ Chronic eosinophilic pneumonia

Diagnosis based on:

- 1) Demonstration of opacities on chest imaging and
- Identification of eosinophilia in peripheral blood, bronchoalveolar lavage fluid, or lung biopsy tissue

Acute eosinophilic pneumonia

Definition

• Chronic eosinophilic pneumonia is an **idiopathic acute** disorder characterized by an abnormal accumulation of eosinophils in the interstitial and alveolar spaces of the lung.

Features

- Acute eosinophilic pneumonia is an acute febrile illness of less than four weeks duration (often less than seven days), a nonproductive cough, and progressively worsening dyspnea.
- malaise, myalgias, night sweats, and pleuritic chest pain.

Association

new onset or resumption of cigarette smoking.

Diagnosis based on:

- Acute febrile illness of short duration (one month or less),
- hypoxemic respiratory failure,
- · diffuse pulmonary opacities on chest radiograph, and
- bronchoalveolar lavage eosinophilia (>25 %), after
- exclusion of infection, vasculitis, or other known precipitants (eg, drugs, irradiation)

Treatment

- In severe hypoxemia or respiratory failure requiring mechanical ventilation \rightarrow methylprednisolone
- Mild to moderate (eg, spo2 >92 %) → oral prednisone

The classic presentation of idiopathic acute eosinophilic pneumonia is the rapid onset of acute respiratory failure in a previously healthy patient. diffuse radiographic opacities, and bronchoalveolar lavage with ≥25 % eosinophils, and absence of infection or other known precipitant.

Chronic eosinophilic pneumonia

Definition

 Chronic eosinophilic pneumonia is an idiopathic chronic disorder characterized by an abnormal accumulation of eosinophils in the interstitial and alveolar spaces of the lung.

Feature

dyspnea, cough, fever, and wheezing over 4 weeks to several months.

Diagnosis

- Chest imaging shows predominantly peripheral or pleural-based opacities described as the "photographic negative" of pulmonary edema, are virtually pathognomonic
- Bronchoalveolar lavage (BAL)
 - ⇒ To look for eosinophilia → cell count showing eosinophilia (≥25 %).
 - ⇒ To exclude infection.
- Infections and drug-induced pulmonary eosinophilia need to be excluded.

Treatment

Prednisolone

Tropical pulmonary eosinophilia

Definition

Tropical pulmonary eosinophilia is an immune hyper-responsiveness to microfilariae
that become trapped in the lungs. It is a clinical manifestation of lymphatic filariasis, a
parasitic infection caused by nematodes (roundworms) such as Wuchereria bancrofti.

Epidemiology

- Seen in endemic areas of lymphatic filariasis (mainly India and South East Asia)
- Occurs more frequently in males than in females

Features

- Dry cough that is frequently paroxysmal and nocturnal.
- Asthma-like attacks → wheezing
- fatigue, malaise, and weight loss,

Diagnosis

- †blood eosinophils
- †serum immunoglobulin E.
- ↑ filarial antibody titers (confirmatory test)

Differential diagnosis

- Tropical pulmonary eosinophilia is distinguished from Loeffler's syndrome by
 - A. the severe and protracted course,
 - B. measurable antibodies against filarial antigens, and
 - C. the therapeutic response to diethylcarbamazine.
 - D. If treated late or left untreated, it can lead to pulmonary fibrosis with chronic respiratory failure.

Treatment

- Diethylcarbamazine for 12 to 21 days.
- Bronchospasm can be managed with bronchodilators and short-term corticosteroids.

The diagnostic criteria for tropical pulmonary eosinophilia include:

- 1) history of residence or travel to a filarial endemic region,
- 2) paroxysmal nocturnal cough with dyspnoea,
- 3) leucocytosis with peripheral blood eosinophilia >3,000/microL,
- 4) elevated serum IgE and an antifilarial antibodies (IgG and IgE) levels,
- 5) pulmonary infiltrations in chest x-ray, and
- 6) clinical improvement with DEC (diethylcarbamazine).

Loffler's syndrome

Definition

Löffler syndrome is a form of eosinophilic pulmonary disease characterized by absent or
mild respiratory symptoms (most often dry cough), transient CXR shadowing and blood
eosinophilia. thought to be due to parasites such as Ascaris lumbricoides (the most
common parasite) causing an alveolar reaction.

Features

· Fever, cough and night sweats which often last for less than 2 weeks.

Diagnosis based on

- Characteristic and often transient respiratory symptoms
- Chest x-ray findings → fleeting migratory pulmonary opacities
- Peripheral blood eosinophilia.
- Exclusion of other types of eosinophilic lung disease (e.g. acute eosinophilic pneumonia

 → severe hypoxemia, and typically a lack of increased blood eosinophils at the onset of disease).

Treatment

- Symptomatic and may consist of corticosteroids.
- Generally, a self-limiting disease, usually resolves within 1 month.

Cryptogenic organising pneumonia (COP)

Definition

- A rare type of inflammatory interstitial lung disease, characterised by a buds of granulation tissue in the alveoli and bronchioles on histopathology
- other names: Bronchiolitis obliterans organising pneumonia (BOOP)

Causes

- Idiopathic: most common 'cryptogenic means unknown cause'.
- Secondary organising pneumonia: connective tissue disease, malignancy, infection, drugs and toxins

Epidemiology

- Typically, age of onset is 50 to 60 years
- · Men and women affected equally.

Feature

Mimic community-acquired pneumonia (eg, cough, dyspnea with exertion, weight loss).

Investigations

- Chest X-ray: bilateral patchy infiltrates
- Chest CT: multiple ground-glass or consolidative opacities that tend to be at the lung periphery

- ⇒ **Reversed halo sign**, better known as an **atoll sign** (a region of ground-glass opacity surrounded by crescentic or annular denser tissue).
- Pulmonary function tests (PFTs) →restrictive pattern

Diagnosis

- Exclusion of any possible cause (e.g. COVID-19 → do PCR)
- For definitive diagnosis → lung biopsy → excessive proliferation or "plugs" of granulation tissue within alveolar ducts and alveoli (Masson bodies). Granulation tissue extends uniformly into the alveolar ducts and does not distort pulmonary architecture, unlike usual interstitial pneumonia.
 - ⇒ If clinical presentation, radiographic appearance and bronchoscopy with bronchoalveolar lavage is consistent with COP, surgical lung biopsy is not required for diagnosis.

Treatment

- 1st line: Prednisolone (usually effective)
- 2nd line: cyclophosphamide or azathioprine

Prognosis

• Relapse is common

Cryptogenic organizing pneumonia (COP)

- High-resolution CT of the chest → bilateral ground-glass opacities
- Exclude other possible causes
- · Persistent pulmonary opacities despite antibiotic treatment.
- Lung biopsy \rightarrow granulation tissue plugs in small airways

Cryptogenic Organizing Pneumonia/https/ncbi.nlm.nih.gov/

Pulmonary hypertension (PH)

Definition

 Sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise, pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance > 3 Wood units.

Epidemiology

more commonly affects female

Pathophysiology: Increased pulmonary vascular resistance

- Occlusive vasculopathy (e.g., PE, connective tissue diseases)
- Hypoxic pulmonary vasoconstriction: chronic hypoxic pulmonary vasoconstriction →
 airway smooth muscle hypertrophy and pulmonary vascular bed destruction →
 pulmonary vascular resistance
- Inflammation (e.g., COPD) → ↑ inflammatory cell infiltration of intima → thickened endothelial wall → intimal fibrosis
- † Increased pulmonary vessel pressure: due to left heart dysfunction
- ↑ endothelin and ↓ vasodilators (e.g., NO, prostacyclin) → vasoconstriction

Causes according to WHO Classification

- Group 1: Pulmonary arterial hypertension (PAH), Idiopathic, familial
 - ⇒ collagen vascular disease, HIV, sickle cell disease
 - \Rightarrow drugs and toxins \rightarrow e.g. **amphetamines**, cocaine (but not heroin).
- Group 2: Pulmonary hypertension with left heart disease
- Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
 - ⇒ COPD, interstitial lung disease, sleep apnoea, high altitude
- Group 4: Pulmonary hypertension due to thromboembolic disease
- Group 5: Miscellaneous conditions: lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

Features

- Exertional dyspnoea is the most frequent symptom
- Symptoms of right ventricular (RV) failure (eg, exertional chest pain or syncope, loud P2, elevated jugular venous pressure, right-sided murmurs, edema, right upper quadrant pain, ascites, and pleural effusion)

Investigations

- Transthoracic echocardiography is the initial test of choice
 - \Rightarrow If left heart disease (LHD) explain the PH \rightarrow RHC is not indicated.
 - ⇒ If no LHD explain the PH → investigate for pulmonary causes
 - Chest CT
 - Pulmonary function testing (PFTs)
 - ventilation-perfusion (V/Q) scanning → chronic thromboembolic disease
 - Obstructive sleep apnoea
 - Autoimmune serologies
 - HIV serology
 - \Rightarrow If pulmonary dysfunction explain the PH \rightarrow RHC is not indicated.
 - ⇒ If pulmonary investigations did not explain the PH → Do RHC
- Right heart catheterization (LHC) is the best investigation for diagnosing pulmonary hypertension
 - \Rightarrow mostly for patients with no cardiac or respiratory causes explaining the PH \rightarrow to evaluate for PAH.
 - ⇒ The diagnosis of primary pulmonary hypertension (PAH) requires RHC that demonstrates mean pulmonary artery pressure (mPAP) >20 mmHg at rest, pulmonary vascular resistance (PVR) ≥3 Wood units, and a mean pulmonary capillary wedge pressure (PCWP) <15 mmHg.
 - ⇒ a mPAP ≥20 mmHg, PCWP ≥15 mmHg, and a normal or reduced cardiac output is consistent with left heart disease-pulmonary hypertension (LHD-PH).
- Pulmonary angiography is the definitive diagnostic test.

Management

- First step: Treat any underlying conditions, for example with anticoagulants or oxygen.
- Second step: perform acute vasodilator testing to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide
 - ⇒ If there is a positive response to acute vasodilator testing → oral calcium channel blockers (nifedipine or extended-release diltiazem)
 - ⇒ If there is a negative response to acute vasodilator testing:
 - endothelin receptor antagonists: bosentan

- phosphodiesterase inhibitors: sildenafil
- prostacyclin analogues: treprostinil, iloprost

Complication

Cor pulmonale (right ventricular failure).

Prognosis

 Pregnant with pulmonary hypertension have a high mortality of 30% - 50% highest immediately after delivery.

Sarcoidosis

Sarcoidosis CXR

- 1 = BHL
- 2 = BHL + infiltrates
- 3 = infiltrates
- 4 = fibrosis

Definition

 Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas.

Epidemiology

- More common in black people (African descent) and subjects of Caribbean origin
 - ⇒ in Europe, sarcoid is commonest amongst Caucasians and has a significantly higher incidence in the Irish.
- More common among females than males $\mathcal{L} > \mathcal{L}$ (2:1)
- Typically affects young adults.
- More common in non-smokers

Pathology

- Noncaseating granulomas in the organ involved.
 - ⇒ the characteristic pathological feature of sarcoidosis.
 - ⇒ may occur anywhere
 - ⇒ The central area of the granuloma will occasionally contain a **Schaumann body**, formed of crystallised material (**calcium phosphate**).
 - ⇒ These granulomas have the capacity to produce 1,25 vitamin D explaining the associated hypercalcaemia.

Features

- Often asymptomatic in the early stages (≈ 50%) → incidental chest x ray finding.
- · Enlargement of lymph nodes
 - ⇒ The most common physical exam finding
- Pulmonary (most common)
 - ⇒ Dry cough
 - ⇒ Dyspnoea (Pulmonary fibrosis)
- Extrapulmonary

- ⇒ Skin lesions: seen in 25 %, often an early finding.
 - Erythema nodosum: tender erythematous nodules on the lower extremities and is a predictor of a good prognosis.
 - lupus pernio: indurated plaques with discoloration of the nose, cheeks, lips, and ears. It is a predictor of a poor prognosis.
- Arthralgia: typically targets the ankle joint.
- ⇒ **Uveitis** (25% of cases): red, painful eyes and blurred vision
- ⇒ Neurologic: (5% of cases) → Cranial nerves (e.g. facial nerve or Bell palsy).
- ⇒ Parotid swelling: (5% of cases)
- ⇒ Löfgren syndrome (LS): a combination of erythema nodosum (EN), hilar adenopathy, migratory polyarthralgia, and fever → has 95 % specificity for sarcoidosis.
- ⇒ Hypercalcaemia: (10% of cases) → nephrocalcinosis and nephrolithiasis.
- ⇒ Systemic symptoms
 - Fever
 - weight loss

Investigations

Sarcoidosis is a diagnosis of exclusion of granulomatous lung diseases, including tuberculosis and histoplasmosis. Occupational history should be taken to exclude both berylliosis and silicosis which can present in a similar manner to sarcoidosis.

Chest x ray

- ⇒ Best initial test
- ⇒ abnormal in 85% of lung sarcoid
- ⇒ may show:
 - bilateral hilar lymphadenopathy.
 - Lung fibrosis typically affects the upper zones

CT scan:

- ⇒ If they have typical findings on a radiograph with a typical clinical presentation (eg, in the context of Lofgren's disease) then a CT scan may not be necessary
- ⇒ It is the best next step after chest x ray in atypical presentation.
- ⇒ demonstrate the degree of fibrosis, micronodules in a subpleural or bronchoalveolar distribution, fissure nodularity and bronchial distortion.
- ⇒ Irregular linear opacities and ground-glass shadowing may also be seen.
- ⇒ If the CT scan is diagnostic, then mediastinoscopy, bronchoscopy or biopsies can
 often be avoided.

Tissue biopsy → Non-caseating granulomas

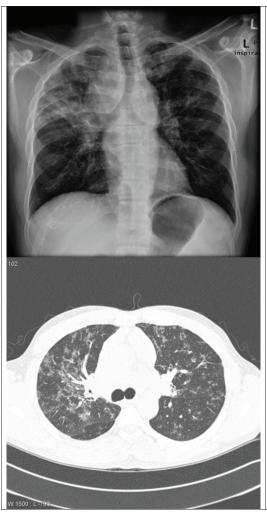
- ⇒ The gold standard test
- ⇒ If the history and radiology is typical, the biopsy is not necessary.
- ⇒ With less characteristic presentations, positive biopsies are needed.
- ⇒ If you are asked to specify the investigation most likely to confirm the diagnosis, only transbronchial biopsy will determine whether non-caseating granulomas are present or not →Transbronchial lung biopsy is therefore the diagnostic investigation of choice.
- ⇒ Skin biopsy for skin lesions

Routine blood tests

- ⇒ **CBC**: Leukopenia in 5-10% of patients
- ⇒ ESR → Elevated

- ⇒ **Creatinine** → elevated in renal involvement
- ⇒ **Electrolytes** → **Hypercalcaemia** (Seen only in 10% if patients)
 - produced by macrophages within the granulomas ↑1-alpha-hydroxylase
 → activates vitamin D → ↑ Ca
- ⇒ Hypergammaglobulinaemia (↑ Immunoglobulins) in 30-80%.
- Exclusion of granulomatous lung diseases
 - ⇒ **TB** should be excluded by sending sputum or BAL washings for AFB
 - A positive tuberculin test in a patient with chronic sarcoidosis is suggestive of active tuberculosis
 - ⇒ Occupational history to exclude both berylliosis and silicosis
- Lung parenchyma involvement → Spirometry
 - ⇒ usually shows a restrictive defect (Decreased gas-transfer factor (TIco) with decreased gas-transfer coefficient (Kco)
- Cardiac involvement
 - ⇒ **ECG:** cardiac sarcoidosis (e.g. heart block →prolonged PR interval)
 - ⇒ Abnormalities in ECG or echocardiogram which suggest cardiac sarcoidosis should be confirmed with cardiac magnetic resonance imaging (CMR) or positron emission tomography (PET).
- CNS involvement → CSF: Intrathecal oligoclonal band production, elevated protein and lymphocytosis
- · Broncho-alveolar lavage
 - ⇒ typically shows a lymphocytosis
 - ⇒ increased CD4+/CD8+ ratio
- ACE levels
 - ⇒ have a sensitivity of 60% and specificity of 70% and are therefore not reliable in the diagnosis of sarcoidosis although they may have a role in monitoring disease activity.
- Kveim test (where part of the spleen from a patient with known sarcoidosis is injected under the skin) is no longer performed due to concerns about cross-infection

The gold standard test \rightarrow transbronchial biopsy \rightarrow noncaseating granulomas



Chest x-ray and CT scan showing stage 2 sarcoidosis with both bilateral hilar lymphadenopathy + interstitial infiltrates.

The reticulonodular opacities are particularly noted in the upper zones.

Remember that pulmonary fibrosis (which this case has not yet progressed to) may be divided into conditions which predominately affect the upper zones and those which predominately affect the lower zones - sarcoidosis is one of the former.

The CT of the chest demonstrates diffuse areas of nodularity predominantly in a peribronchial distribution with patchy areas of consolidation particularly in the upper lobes.

There is some surrounding ground glass opacities. No gross reticular changes to suggest fibrosis.

Staging of chronic sarcoidosis

Stage	Finding	Likelihood of spontaneous resolution
0	Normal chest radiograph	>90%
I	Bilateral hilar lymphadenopathy (BHL)	60-90%
П	BHL plus pulmonary infiltrates	40-60%
III	Pulmonary infiltrates (no BHL)	10-20%
IV	Pulmonary fibrosis (+/- bullae)	<20%

Differential diagnosis of bilateral hilar lymphadenopathy

- Sarcoidosis
- Tuberculosis
- Malignancy including lymphoma
- Cystic fibrosis
- · Churg Strauss disease
- HIV
- · Extrinsic allergic alveolitis
- Phenytoin
- Pneumoconiosis, especially berylliosis. Exposure to beryllium is seen in the nuclear power, telecommunications, semi-conductor and electronics industries.

Management

The majority of patients with sarcoidosis get better without treatment

- Mild disease (Patients with asymptomatic and stable stage 2 or 3 disease who have only mildly abnormal lung function) → NO treatment
 - ⇒ Sarcoidosis remits without treatment in approximately two-thirds of people
- Moderate to severe disease
 - ⇒ First-line → **Prednisolone.** Indications for steroids:
 - patients with chest x-ray stage 2 or 3 disease who have moderate to severe
 or progressive symptoms.
 - Systemic involvement: hypercalcaemia, eye, heart or neuro involvement
 - ⇒ Second-line: Methotrexate is the first choice of second-line agent.
 - ⇒ Third-line: Infliximab given in combination with methotrexate or azathioprine
 - ⇒ Lung transplantation should be considered in all patients with advanced pulmonary fibrosis and associated pulmonary hypertension.

Prognosis

Erythema nodosum is associated with a good prognosis in sarcoidosis.

- · Factors associated with a good prognosis
 - ⇒ HLA B8
 - ⇒ Lofgren's syndrome (bilateral hilar lymphadenopathy, erythema nodosum, polyarthritis and fever).
- Factors associated with poor prognosis
 - ⇒ insidious onset, symptoms > 6 months (chronic pulmonary involvement)
 - ⇒ absence of erythema nodosum
 - ⇒ extrapulmonary manifestations: e.g.
 - lupus pernio: a chronic raised indurated (hardened) lesion of the skin, often purplish in colour, and is associated with sarcoid.
 - Splenomegaly
 - Cardiac involvement: Cardiac sarcoidosis is rare but can manifest as a prolonged PR interval.
 - Chronic hypercalcaemia
 - Nasal mucosal involvement
 - Neurosarcoidosis
 - ⇒ CXR: stage III-IV features
 - ⇒ black people (Afro-Caribbean or Afro-American race)
 - ⇒ Age of onset >40 years

Lofgren's syndrome

Lofgren's syndrome: a variant of sarcoidosis with acute clinical presentation with tetrad of:

- Migratory polyarthritis (acute arthritis), most commonly involves ankles (>90 %).
- 2. Erythema nodosum.
- 3. Bilateral hilar lymphadenopathy.
- 4. Fever.

Overview

- Seen in less than 5 -10 % of sarcoidosis
- Typically, more common in Scandinavian patients and less common in Afro-Caribbean patients
- Typically occurs in young females
- Carries an excellent prognosis
- · Usually self-limiting

Other sarcoidosis variants

Heerfordt syndrome: a variant of sarcoidosis with chronic clinical presentation with tetrad of:

- 1. Parotitis
- 2. Uveitis
- 3. Facial palsy
- 4. Fever

Yellow nail syndrome

Definition

 Yellow nail syndrome is an uncommon disorder characterized by the triad of pulmonary disease, lymphedema, and yellow nails

Features

- Nails are yellow, thickened, curved, with loss of the lunula and cuticle. and may become
 detached from the nail bed.
- Congenital lymphoedema
- Pulmonary disease (bronchiectasis, pleural effusions)
- Chronic sinusitis



Hepatopulmonary syndrome (HPS)

Definition

 oxygenation defect induced by <u>pulmonary vascular dilatation</u> in patients with liver cirrhosis or portal hypertension.

Mechanism

• The vascular dilatation is thought to be induced by increased pulmonary levels of nitric oxide.

Prevalence

• It is seen in 15-30% of patients with cirrhosis.

Features

- Dyspnoea
- Platypnoea (dyspnoea whilst standing) and Orthodeoxia (hypoxaemia exacerbated by being upright) are characteristic
 - ⇒ Due to the predominance of vascular dilatation in the lung bases. Blood flow to these areas is increased in the upright position.
 - ⇒ Hepatic disease → intrapulmonary vasodilatation mainly in the lower Lobes → right-to-left shunting (similar to pulmonary arteriovenous malformations) → increased blood flow through the lower lobes when the patient moves from the supine to the erect position → blood from the lower lobes, which is more poorly oxygenated, entering the left side of the heart → oxygen desaturation in the erect position.

Investigations

- The diagnosis of HPS can only be made in a patient who has liver disease, impaired oxygenation, and intrapulmonary shunt when other etiologies have been excluded.
- Contrast-enhanced <u>transthoracic echocardiography</u> is the best test to demonstrate <u>intrapulmonary vascular dilatation</u>. It can also exclude intracardiac shunting which may result in similar signs and symptoms to hepatopulmonary syndrome.

- - performed by injecting agitated saline intravenously during transthoracic echocardiography.
- - In a normal subject microbubbles are visualised in the <u>right ventricle</u> within seconds, which are then absorbed in the alveoli.
 - Immediate visualization in the <u>left ventricle</u> (within three cardiac cycles) indicates <u>intracardiac shunting</u>.
 - <u>Delayed visualisation in the left ventricle</u> (3-6 cardiac cycles) is diagnostic of <u>intrapulmonary shunting</u>.
- Impaired oxygenation is confirmed when an arterial blood gas analysis demonstrates an
 alveolar-arterial (A-a) oxygen gradient ≥15 mmHg or an arterial oxygen tension (PaO₂)
 <80 mmHg (10.7 kPa)
- Chest imaging and pulmonary function testing are often normal

Treatment

• Liver transplantation is the only proven beneficial available treatment, with 85% of patients showing resolution or significant improvement in gas exchange postoperatively.

Prognosis

It is a poor prognostic indicator.

Pulmonary alveolar microlithiasis (PAM)

Definition

 Pulmonary alveolar microlithiasis (PAM) is a rare, autosomal recessive disorder, characterized by widespread deposition of calcium phosphate microliths throughout the lungs.

Epidemiology

PAM has the highest prevalence in Turkey, Japan, and Italy

Pathophysiology

- It occurs in the absence of disorders of calcium metabolism.
- SLC34A2 gene mutations → ↓ activity of the type IIb sodium-phosphate cotransporter (which located mainly in alveolar type II cells) → accumulation of phosphate in the alveoli → formation of microliths
- SLC34A2 gene is responsible for the uptake of phosphate released from phospholipids in outdated surfactant.

Feature

- Most patients are asymptomatic despite striking radiological abnormalities. often found incidentally during imaging studies for another reason.
- · Symptoms included dyspnea, nonproductive cough, chest pain

Diagnosis

- Chest x-ray: 'sandstorm-appearing' is a typical diagnostic finding (diffuse scattered micronodules, often obscuring the contours of the heart and diaphragm)
- · HRCT: micronodular calcifications, diffuse ground glass opacities
- Bronchoalveolar lavage (BAL) and transbronchial biopsy can be useful if the diagnosis is uncertain.
 - ⇒ BAL and biopsy show the characteristic calciospherocitis (microliths) in the alveoli (deposition of calcium and phosphate crystals).

Treatment

- There is no established therapy for PAM.
- lung transplantation is the only effective therapy.

Pulmonary Alveolar Proteinosis (PAP)

Definition: A rare diffuse lung disease characterized by the progressive accumulation of surfactant protein in the alveoli, that characteristically stain for periodic acid-Schiff (PAS)

Epidemiology: Common in males (M: F = 4:1), the typical age at presentation is 40 to 50 years.

Pathophysiology: \downarrow alveolar macrophages $\rightarrow \downarrow$ ability to remove surfactant $\rightarrow \uparrow$ surfactant accumulation in the alveoli.

Causes

- Autoimmune: due to granulocyte macrophage-colony stimulating factor (GM-CSF) antibodies, the most common
- congenital
- Secondary: chronic infections, immunosuppressants, organic dusts, malignancies.

Feature

progressive dyspnea, cough, sputum production, fatigue, and weight loss

Diagnosis

- Chest x-ray: bilateral symmetric alveolar opacities located centrally in mid and lower lung zones, sometimes resulting in a "bat wing" distribution.
- High resolution computed tomography (HRCT): ground-glass opacification that typically spares the periphery and may have a "crazy-paving" appearance due to thickening of the interlobular and intralobular septa.
- Spirometry → shows a restrictive pattern (↓lung capacity, ↓CO diffusion)
- Autoantibodies : ↑ autoantibody against GM-CSF in serum and BAL fluid
- Flexible bronchoscopy with broncho-alveolar lavage (BAL)
 - ⇒ The standard diagnostic test
 - ⇒ PAS-positive stains

Treatment

- Whole lung lavage: excess surfactant is removed from the lungs via saline solution; may require repeated application
- Treatment of the underlying condition

Carbon monoxide poisoning

Confusion, pyrexia and pink mucosae are typical features of carbon monoxide poisoning

Carbon monoxide poisoning - most common feature = headache

Epidemiology

Carbon monoxide is the commonest cause of poisoning-associated death in UK

Causes

- House fires
- Wood-burning stoves
- Furnaces in enclosed and poorly ventilated spaces. Often involves multiple individuals (e.g., family) during the winter
- Fumes from cleaning fluids and paint removers that contain methylene chloride (dichloromethane) can also cause carbon monoxide poisoning. When breathed in, methylene chloride is converted into CO gas.

Pathophysiology

- The affinity of hemoglobin for CO is ~ 240 times stronger than for O2 → formation of COHb
 (carboxyhemoglobin)→ ↓ oxygen-carrying capacity of hemoglobin → tissue hypoxia
- COHb →Shift the O2 dissociation curve to the left → ↑ affinity for O2 → ↓ release of O2 in tissue

Questions may hint at badly maintained housing e.g. student houses

Features of carbon monoxide toxicity

- Nonspecific symptoms
 - ⇒ Headache: the most common symptom ≈ 90% of cases

 - ⇒ Fatique
 - ⇒ Nausea/vomiting
- Neurotoxicity
 - ⇒ Altered mental status (e.g., agitation, confusion, somnolence, memory loss)
 - ⇒ Seizures
 - ⇒ Loss of consciousness/coma
 - Cerebellar signs are the most reliable indicator of significant neurological toxicity
- Cardiorespiratory toxicity
 - ⇒ Inhalation of hot smoke → upper airways burn → mucosal swelling → Bronchoscopy is the best tool to establish whether there is significant oedema or mucosal ulceration obstructing the airways.
 - ⇒ hypertension, tachycardia
 - ⇒ Shock
- COHb levels have prognostic implications, which are summarised here:

- ⇒ < 30% cause only headache and dizziness
- ⇒ 40–60% produces syncope, tachypnoea, tachycardia and fits
- ⇒ 60% cause an increasing risk of cardiorespiratory failure and death.

Suspect carbon monoxide poisoning when multiple people from the same confined household complain of the headache and fatigue.

Diagnosis

- Arterial blood-gas analysis
 - ⇒ Typical carboxyhaemoglobin (COHb) levels:
 - < 3% non-smokers</p>
 - < 10% smokers</p>
 - 10 30% symptomatic: headache, vomiting
 - >30% severe toxicity
 - ⇒ PaO2: usually appears normal
- Direct spectrophotometric measurement of Carboxyhaemoglobin (COHb) in a bloodgas analyser is the gold standard.
 - ⇒ A bedside HbCO oximeter is now available
- ECG and cardiac monitor for all patients for 4 − 6 hours → signs of myocardial ischemia; arrhythmias

Pulse oximeters cannot distinguish between COHb and HbO2. Pulse oximetry appears normal because carboxyhaemoglobin has similar absorption spectra to oxyhaemoglobin.

Management

- First-line: 100% oxygen → Give high-flow oxygen (12 l/min) via a tight-fitting mask without a re-breathing circuit
- Second-line: hyperbaric oxygen
 - ⇒ shorten the washout of COHb, but access and transfer times to a hyperbaric chamber can make this not practical.
 - ⇒ Indications for hyperbaric oxygen
 - CO level >25 %
 - Loss of consciousness
 - Severe metabolic acidosis (pH <7.1)
 - Evidence of end-organ ischemia (eg, ECG changes, chest pain, altered mental status)
 - pregnancy
- In severe cases intubation and mechanical ventilation may be required

Carbon monoxide (CO) poisoning

Pathophysiology → increased affinity of carbon monoxide with haemoglobin results in tissue hypoxia

The most common symptom is → headache

Standard pulse oximetry (SpO2) is unable to distinguish between oxyhemoglobin and COHb.

Diagnosis: blood gas analysis to confirm the diagnosis based on the carboxyhaemoglobin (COHb) level.

- < 3% → non-smokers
 </p>
- 10 30% → symptomatic: headache, vomiting
- > 30% → severe toxicity

Treatments:

- Mild to moderate →100% high-flow oxygen via a nonrebreather mask
- <u>Sever:</u> COHb > 30%, complicated with CNS or cardiac events or pregnancy → hyperbaric oxygen PassOnExam

Smoking cessation

Action of smoking

- Nicotine is a stimulant and releases dopamine in the brain that leads to addictive effects of smoking.
- Its effects can be replaced in other ways using nicotine replacement therapy and this reduces the addiction to cigarette smoking.

General points of treatment

- · Advise all people who smoke to stop
- Offer referral to a local smoking cessation service for behavioural support and drugs (a combination of drug treatment and behavioural support may be the best option)
- Advise to stop abruptly.
- Patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion.
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- If unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- Do not offer NRT, varenicline or bupropion in any combination
- Starting date of the treatment
 - ⇒ Start NRT on the guit date.
 - ⇒ Start varenicline or bupropion 7-14 days before the quit date.
- Duration of treatment
 - ⇒ Prescribe NRT for 2 weeks after stop date
 - ⇒ Prescribe varenicline or bupropion FOR 3- 4 weeks after stop date.
- Varenicline or combination NRT (a patch plus a short-acting preparation) have been shown to be the most effective treatments.
- Varenicline or bupropion should not be prescribed to pregnant or breastfeeding women or young people aged under 18.
- No one form of NRT is more effective than another.
- Reviewed 2 weeks after stopping smoking, and the CO level measured at 4 weeks.

Nicotine replacement therapy (NRT)

- Available in a choice of formats, including Gum, Inhalator, Sublingual tablet, Nasal and Oral spray, and Transdermal patch
- Nice recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past.

Duration

- ⇒ The duration of treatment with NRT is 8–12 weeks (depending on which form of NRT is used and which dose is initiated), followed by a gradual reduction in dose.
- ⇒ For children over the age of 12 years, treatment should be limited to 12 weeks.
- ⇒ Treatment with NRT can be stopped abruptly or tapered gradually
- No absolute contraindications
- Adverse effects: Headache, dizziness, Nausea, vomiting, Rash, urticaria.

Varenicline

- **Mode of action:** a partial nicotinic receptor agonist → reduces the rewarding and reinforcing effects of smoking by preventing nicotine binding to the receptors.
- Duration
 - ⇒ Advise the person to stop smoking 7–14 days after starting varenicline.
 - ⇒ The recommended course of treatment is 12 weeks.
 - ⇒ Varenicline may be stopped without tapering the dose. However, immediately after stopping treatment with varenicline, up to 3% of people experience an increase in irritability, urge to smoke, depression, or insomnia. Consider tapering the dose in these people.

Contraindications

- ⇒ Aged under 18 years.
- ⇒ Pregnancy.
- ⇒ End-stage renal disease.
- Common adverse effects
 - ⇒ **Nervous system:** headache; somnolence, dizziness, dysgeusia.
 - ⇒ **Psychiatric:** abnormal dreams, insomnia
 - ⇒ GIT upset and dry mouth

Bupropion

- Mode of action: selective dopamine and noradrenaline re-uptake inhibitor
- Duration
 - ⇒ Advise the person to stop smoking 7–14 days after starting bupropion.
 - ⇒ If no effect is seen after 7 weeks, discontinue treatment with bupropion.
 - Contraindications
 - ⇒ Age under 18 years
 - ⇒ Pregnancy
 - ⇒ History of seizures.
 - ⇒ CNS tumour.
 - ⇒ History of bulimia or anorexia nervosa.
 - ⇒ History of bipolar disorder.
 - ⇒ Severe hepatic cirrhosis.
 - Common adverse effects
 - ⇒ **Psychiatric**: insomnia, depression, agitation, anxiety
 - ⇒ Nervous system: tremor, concentration disturbance, headache, dizziness, taste disorders.
 - ⇒ GIT upset and dry mouth

Bupropion: contraindicated in epilepsy

Medications used for Smoking cessation

	NRT	Varenicline	Bupropion
Action	Nicotine replacement therapy	partial nicotinic receptor agonist	Norepinephrine and dopamine reuptake inhibitor
Effectiveness	Effective with combination of two forms of NRT	Effective	Less effective than NRT and Varenicline
Date of starting	on the quit date	7–14 days before quit date.	7–14 days before quit date
Duration	8-12 weeks	12 weeks	7 weeks
Absolute contraindications	NO absolute contraindications	 Aged < 18 years Pregnancy End-stage renal disease 	 Age < 18 years Pregnancy History of seizures CNS tumour bulimia or anorexia nervosa bipolar disorder Severe hepatic cirrhosis
Prescribe with Cation	 Chronic diseases (DM, HTN, RF, MI, CVA) Epilepsy. 	 Cardiovascular, renal & psychiatric illness. Epilepsy 	 Conditions lower the seizure threshold (e.g. Alcohol abuse, head trauma, diabetes, antipsychotics). Hepatic & renal impairment.
Common adverse effects	Headache, dizziness, Nausea	Headache, abnormal dreams, insomnia & GI upset	Headache, insomnia, depression, tremor.

Pregnant women

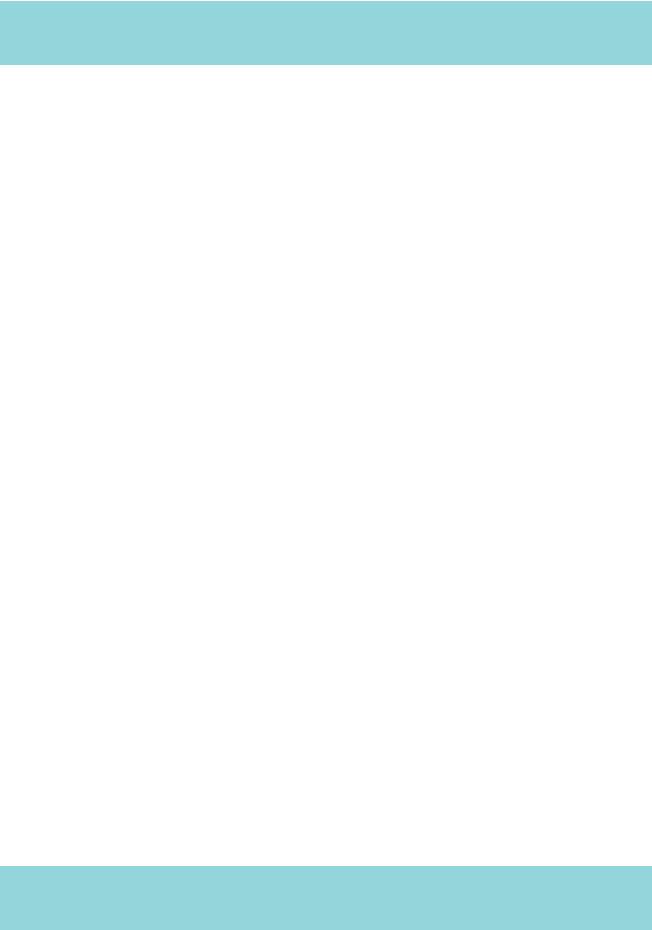
Assessment

- ⇒ NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide detectors, partly because 'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'
- ⇒ All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

Adverse effects of smoking in pregnancy

- ⇒ Reduces birth weight
- ⇒ increases risk of miscarriage and still birth.
- ⇒ The infant has a greater risk of sudden infant death syndrome.
- ⇒ affect ovarian function in female children.

- ➡ increases lung maturity, possibly by enhancing the production or secretion of cortisol. This makes neonates less likely to develop respiratory distress syndrome, but as lung maturation is often abnormal babies may have reduced lung function and increased rates of other respiratory illnesses.
- Interventions in pregnant smoker
 - ⇒ first-line: cognitive behaviour therapy and support from stop Smoking Services
 - ⇒ second line: NRT
 - NRT should only be used if smoking cessation without NRT fails.
 - Pregnant women should remove the patches before going to bed
 - ⇒ varenicline and bupropion are contraindicated



Third edition

Notes & Notes

For MRCP part 1 & 11

By

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Gastroenterology

Updated 2021

Oesophageal diseases

Achalasia

Definition

 Failure of oesophageal peristalsis and of relaxation of lower oesophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e. LOS contracted, oesophagus above dilated.

Pathophysiology

 Atrophy of inhibitory neurons in the Auerbach plexus → lack of inhibitory neurotransmitters (e.g., NO, VIP) → inability to relax and increased resting pressure of the LES, as well as dysfunctional peristalsis → esophageal dilation proximal to LES

Epidemiology

- prevalence of around 10 /100,000 persons.
- typically presents in middle-age
- · equally common in men and women.

Causes

- Primary achalasia (most common): cause is unknown
 - Secondary achalasia (pseudoachalasia):
 - ⇒ mechanical obstruction (e.g., a malignancy)
 - ⇒ Chagas disease

Features

- · Symptoms usually develop years before the patient presents
- Dysphagia of BOTH liquids and solids.
- Regurgitation of food → heartburn, cough, aspiration pneumonia etc
- Oesophageal spasm → vague chest discomfort (common)
- · Weight loss

Complications

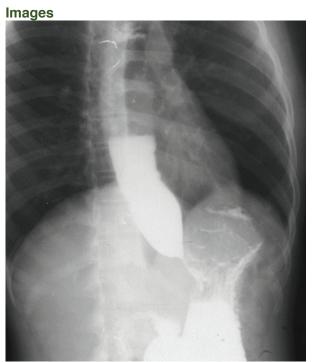
· Increased risk of esophageal cancer.

Investigations

- · Barium swallow
 - ⇒ initial investigation
 - ⇒ will show: dilated oesophagus, fluid level, 'bird's beak' appearance
- Manometry:
 - ⇒ The confirmatory test of choice
 - ⇒ Will show:
 - excessive LOS tone which doesn't relax on swallowing
 - Lack of peristalsis in the lower two-thirds of the esophagus
- Upper endoscopy
 - ⇒ to rule out pseudoachalsia
 - ⇒ Usually normal, May show retained food in esophagus or increased resistance of LES during passage with endoscope
- CXR: Will show:
 - ⇒ wide mediastinum, (>6 cm on an upright PA chest X-ray or > 8 cm on supine AP chest film).
 - ⇒ fluid level

Treatment

- **Heller cardiomyotomy** (Laparoscopic myotomy)
 - ⇒ The best initial treatment for most patients with achalasia.
- Balloon dilation (Pneumatic dilatation)
 - the preferred option for older unfit patients or patients who choose a nonsurgical treatment.
 - Current guidelines recommend obtaining <u>gastrograffin study</u> followed by barium esophagram in all patients after pneumatic dilation to exclude esophageal perforation
 - ⇒ long-term efficacy is less than that of surgical myotomy. 25% of patients treated with pneumatic dilation required re-dilation.
- Intra-sphincteric injection of botulinum toxin
 - ⇒ Reserved for the elderly and who cannot tolerate dilatation or surgery.
 - ⇒ Reduces the LOS pressure and provides symptomatic relief. However, the effects are temporary, and patients need to undergo repeat injections every six to twelve months.
- Drug therapy has a role but is limited by side-effects
 - ⇒ Short-term improvement in clinical symptoms may occur with isosorbide mononitrate, a long-acting nitrate or with nifedipine, a calcium-channel blocker.
- Contraindications
 - ⇒ Promotility agents like metoclopramide increase the lower oesophageal sphincter pressure and so are contraindicated in achalasia.



This film demonstrates the classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis



Mediastinal widening secondary to achalasia. An air-fluid level can sometimes be seen on CXR but it is not visible on this film



Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

TOP TIPS

Dysphagia affecting both solids and liquids from the start - think achalasia

The gold standard test for achalasia is oesophageal manometry

The most appropriate initial investigation of a high dysphagia is a barium swallow, which identifies the site of pathology and forewarns of pitfalls such as a pharyngeal pouch, which if unidentified can increase the risk of perforation at endoscopy.

Dysphagia

The table below gives characteristic exam question features for conditions causing dysphagia:

Diagnosis	Characteristic features
Oesophageal cancer	 Dysphagia may be associated with weight loss, anorexia or vomiting during eating Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use
Oesophagitis	 May be history of heartburn Odynophagia (Painful swallowing) but no weight loss and systemically well
Oesophageal candidiasis	 There may be a history of HIV or other risk factors such as steroid inhaler use Treatment → oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days).
Achalasia	 Dysphagia of both liquids and solids from the start Heartburn Regurgitation of food - may lead to cough, aspiration pneumonia etc
Pharyngeal pouch	 More common in older men Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles Usually not seen but if large then a midline lump in the neck that gurgles on palpation Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. Halitosis may occasionally be seen
Systemic sclerosis	Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, oesophageal dysmotility, Sclerodactyly, Telangiectasia As well as oesophageal dysmotility the lower oesophageal sphincter (LES) pressure is decreased. This contrasts to achalasia where the LES pressure is increased
Myasthenia gravis	Other symptoms may include extraocular muscle weakness or ptosis Dysphagia with liquids as well as solids
Globus hystericus	 May be history of anxiety Symptoms are often intermittent and relieved by swallowing Usually painless - the presence of pain should warrant further investigation for organic causes

Classification	Examples
Extrinsic	Mediastinal massesCervical spondylosis
Oesophageal wall	AchalasiaDiffuse oesophageal spasmHypertensive lower oesophageal sphincter
Intrinsic	TumoursStricturesOesophageal webSchatzki rings
Neurological	 CVA Parkinson s disease Multiple Sclerosis Brainstem pathology Myasthenia Gravis

Dysphagia

- Dysphagia to both solids and liquids → Achalasia (motility disorder)
- Dysphagia to solids only → Oesophageal obstruction (structural disorder, e.g. malignancy)

Investigations

• Barium contrast oesophagram is the **initial test** (prior to upper endoscopy)

Oesophageal disorders

The table below lists a small group of oesophageal disorders that are not covered elsewhere in the notes.

Disorder	Notes
Plummer- Vinson syndrome	Triad of:
Mallory-Weiss syndrome	Severe vomiting → painful mucousal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics
Boerhaave syndrome	Severe vomiting → oesophageal rupture

Oesophageal web

Oesophageal web		
What is it?	a thin mucosal membrane projecting into the lumen → oesophageal constriction	
Common age and gender?	middle-aged females	
Common symptoms?	dysphagia and regurgitation of food	
Common location?	 in the cervical oesophagus near cricopharyngeus muscle. Typically arise from the anterior wall and never from the posterior wall. 	
Associations?	 Plummer-Vinson syndrome graft-versus-host disease gastroesophageal reflux disease external beam radiation 	
Investigation of choice?	Barium swallow	
Consequences?	DysphagiaSquamous cell carcinoma	

Diffuse oesophageal spasm

- Features
 - ⇒ Dysphagia
- Diagnosis
 - ⇒ barium swallow demonstrates a 'corkscrew appearance'
 - ⇒ Manometry reveals:
 - prolonged, repetitive and high amplitude contractions.
 - The lower oesophageal sphincter pressure is increased and there is incomplete relaxation of the sphincter.

Differential diagnosis manometry findings:

- Absence of peristalsis in the body of the oesophagus + high lower oesophageal sphincter
 → Achalasia
- Normal contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → Hypertensive lower oesophageal sphincter
- High amplitude contractions in the body of the oesophagus + high lower oesophageal sphincter pressure → Diffuse oesophageal spasm

Gastro-oesophageal reflux disease (GORD)

Definition: regurgitation of stomach contents into the esophagus

Pathophysiology

- Decreased tone of the lower esophageal sphincter.
- The most important physiological mechanism that prevents reflux →
 Parasympathetic stimulation of the lower circular smooth-muscle fibres of the
 oesophagus

Cause

- Transient lower esophageal sphincter relaxation is the most common cause
- Pregnancy → decreased motility secondary to progesterone
- · gastric acidity
- gastric outlet obstruction
- decreased esophageal motility
- hiatal hernia: ≥ 90% of patients with severe GORD
- Obesity →Transient relaxations of the lower esophageal sphincter (TRLES). The main stimulus for TRLES is gastric distension, particularly in the fundus.
- Lifestyle habits such as smoking, caffeine and alcohol consumption
- Scleroderma
- Angle of His enlargement (> 60°)

Features

- · Heartburn and regurgitation when lying down.
- GORD is the most common non-cardiac cause of **chest pain**.
- Extraesophageal symptoms (eg. chronic cough, hoarseness, wheezing)
 - ⇒ The three most common causes of a persistent cough are postnasal drip, asthma, and GORD.
- Acid reflux in chronic GORD can lead to damage of the enamel layer of teeth.
- May present with over-the-counter antacids side effects which may include magnesium hydroxide.
 - Magnesium hydroxide can act as an osmotic laxative, resulting in the adverse effect of diarrhea.

Investigations

- Endoscopy: Indications for upper GI endoscopy:
 - ⇒ No symptomatic improvement after PPI trial
 - ⇒ Alarm features
 - New onset dyspepsia in patient ≥60 years
 - Dysphagia
 - Odynophagia
 - Early satiety
 - Persisting vomiting
 - Unintentional weight loss
 - Aspiration pneumonia
 - Evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia, occult blood in stool)
 - Iron deficiency anemia
 - Anorexia
 - Gastrointestinal cancer in a first-degree relative
 - ⇒ The most common endoscopic finding is reflux esophagitis.
 - ⇒ Symptoms do not correlate with mucosal status at endoscopy appearance
- 24-hr oesophageal pH monitoring: If endoscopy is negative (the gold standard test for diagnosis)
 - ⇒ To confirm the diagnosis of GORD in patients with persistent symptoms of GORD despite a trial of PPI therapy.
 - ⇒ Evaluation before surgical or endoscopic antireflux procedure
- Oesophageal manometry
 - ⇒ In patients with suspected GORD and a normal upper endoscopy to exclude an esophageal motility disorder.
 - ⇒ To evaluate esophageal peristaltic function prior to antireflux surgery.

Treatment

- Lifestyle changes
 - ⇒ Small portions;
 - ⇒ avoid eating (< 3 hours) before bedtime.
 - ⇒ Avoid foods with high fat content
 - ⇒ Avoid: nicotine, alcohol, coffee, and certain drugs (e.g., calcium channel blockers, diazepam)
- Pharmacological: if lifestyle changes are ineffective
 - ⇒ Proton pump inhibition (PPI):
 - full-dose PPI (e.g. 20 mg omeprazole OD) for 4 or 8 weeks.
 - In those failing to respond to two months of full dose therapy doubling the dose of proton pump inhibitor for one month increases response rate.
 - If no response, increase the dose to (twice daily therapy)
 - If symptoms recur after initial treatment, offer a PPI at the lowest dose possible to control symptoms.
 - ⇒ H2 receptor antagonist
 - The 2nd line if there is an inadequate response to a PPI
 - In those failing to respond to a double dose of proton pump inhibition an <u>H2</u>
 <u>receptor</u> antagonist may be added <u>or substituted</u> in treatment <u>or a</u>
 prokinetic agent added to treatment.
- Laparoscopic Nissen fundoplication
 - ⇒ the treatment of choice for patients with GORD refractory to or intolerant of proton pump inhibitor therapy.
 - ⇒ The patient should have had an endoscopy within the six months prior to surgery to exclude any unsuspected pathology such as Barrett's oesophagus or adenocarcinoma.
 - $\Rightarrow \,$ the most useful in assessing the role of surgery \rightarrow Oesophageal motility and pH study
- Severe oesophagitis
 - ⇒ 1st line: full-dose PPI (e.g. omeprazole 20 mg OD) for 8 weeks
 - ⇒ 2nd line: high dose PPI (double standard dose e.g. 40 mg omeprazole OD) of the initial PPI, switching to another full-dose PPI or switching to another high-dose PPI
 - ⇒ Maintenance treatment → long-term full-dose PPI.
 - ⇒ If fail to respond to maintenance treatment, → switch to another PPI at full dose or high dose.
- Management of GORD in pregnancy includes
 - ⇒ 1st line: lifestyle and dietary modification
 - ⇒ 2nd line: antacids and sucralfate. Antacids containing sodium bicarbonate and magnesium trisilicate should be avoided in pregnancy.
 - ⇒ 3rd line: similar to nonpregnant patients, H2RAs and then PPIs.

Complications

- Barrett esophagus: Metaplasia of the lower esophagus
- Esophageal strictures occur in 10%
 - ⇒ Two types of rings (**Schatzki rings**):muscular ring, or A ring: located approximately 2 cm above the gastroesophageal junction. Rare
 - ⇒ mucosal ring, or B ring: most common. located at the squamo-columnar junction.
 - ⇒ mechanical cause of dysphagia
 - ⇒ most patients respond well to dilatation therapy.
 - ⇒ People who have had dilatation of an oesophageal stricture should remain on longterm full-dose PPI therapy
- Adenocarcinoma of the lower esophagus.

GORD management

- 1st line → lifestyle changes
 - ⇒ don't lie down after eating
 - ⇒ avoid spicy foods
 - ⇒ eat small servings
- 2nd line → proton pump inhibitors (omeprazole, lansoprazole) for at least 8 weeks (once daily therapy)
 - ⇒ No response: → further diagnostic evaluation
 - ⇒ Partial response: → increase the dose to (twice daily therapy)
 - ⇒ Good response: → discontinue PPI after 8 weeks
 - ⇒ If symptoms recur after discontinuation of PPIs → Maintenance therapy
 - ⇒ After 8 weeks of initial treatment, reduce PPI to lowest effective dose
- **3rd line** → H2 receptor antagonists(cimetidine, ranitidine)
- 4th line → Surgical Nissen fundoplication or hiatal hernia repair

Barrett's oesophagus

Overview

- Metaplasia of the lower oesophageal mucosa 1 cm or more proximal to the gastroesophageal junction. (the normal squamous epithelium of the oesophagus replaced by a columnar epithelium) (ie, intestinal metaplasia)
- The physiological transformation zone ("Z-line") between squamous and columnar epithelium is shifted upwards
- Metaplasia is defined as the replacement of one type of cells with another type whereas dysplasia is the disordered growth of the cells.
- Barrett esophagus is a premalignant condition of the lower esophagus caused by chronic esophageal reflux
- the columnar epithelium may resemble that of either the cardiac region of the stomach or that of the small intestine (e.g. with goblet cells, brush border)

Risk factors

- Age > 50 years
- Male gender
- Ethnicity: more common in white populations than Hispanic, Black, or Asian.
- Long duration or frequency of Gastro-oesophageal reflux disease (GORD) symptoms
- Previous oesophagitis
- Hiatus hernia
- · Central obesity

Diagnosis

- Endoscopic evaluation, with:
 - ⇒ Visualization of columnar epithelium 1 cm or more above the gastroesophageal junction
 - ⇒ Biopsy sampling of esophageal epithelium with histologic confirmation of intestinal metaplasia (American guidelines) or histologic confirmation of columnar epithelium (British guidelines).

Management (based on presence or absence of dysplasia)

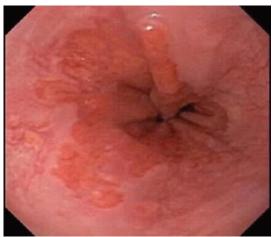
Nondysplastic: proton pump inhibitors + surveillance endoscopy with repeated biopsy every 3 to 5 years

- NO dysplasia and <3 cm segment of Barrett's → endoscopy every three to five years with biopsies</p>
- ⇒ **NO** dysplasia <u>and</u> segment Barrett's >3 cm → Endoscopy every two to three years
- Low-grade dysplasia (LGD)
 - ⇒ Repeat endoscopic biopsy in 6 months. If LGD is found → Radiofrequency ablation
 - ⇒ If ablation is not undertaken, 6-monthly surveillance is recommended
- Moderate to high grade dysplasia or recurrent disease
 - ⇒ 1st line: Endoscopic ablation therapy (endoscopic resection of any visible mucosal irregularities, followed by **Radiofrequency Ablation (RFA)** to ablate the remaining metaplastic epithelium.)
 - ⇒ 2nd line: Oesophagectomy
- High-dose proton pump inhibitor:
 - ⇒ The best next line of management
 - ⇒ whilst this is commonly used in patients with Barrett's the evidence base that this reduces the change of progression to dysplasia or induces regression of the lesion is limited

Histology at biopsy	Endoscopy frequency	Actions
No dysplasia	Every 2 - 5 years	
Low-grade dysplasia		Repeat endoscopy with quadrantic biopsies every 1cm.
High-grade dysplasia	Every 3 months	If a visible lesion is present, consider endoscopic ablation with mucosal resection (EMR) or radiofrequency ablation.

Prognosis

↑↑ risk of oesophageal adenocarcinoma (50-100 fold), although the absolute risk is low (< 1%).



Barrett's oesophagus

Oesophagitis in immunosuppressive patients

Causes

- Candidal esophagitis is the most common cause of symptomatic disease.
- Ulcerative esophagitis resulting from cytomegalovirus is the next most important etiologies.
 - ⇒ Cytomegalovirus (CMV) most commonly causes multiple ulcers at the lower esophageal sphincter
- Herpes simplex virus esophagitis appears to be relatively uncommon.

Features

• The hallmark of oesophagitis is odynophagia or pain on swallowing.

Diagnosis

Endoscopy with a biopsy

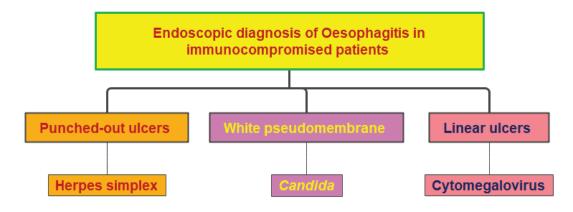
Treatment

- Candida spp.
 - ⇒ Nonpregnant patients, we suggest initial therapy with fluconazole
 - ⇒ Pregnant patients → amphotericin B is the treatment of choice during the first trimester since oral azoles are teratogenic.
- Herpes simplex virus (HSV) → oral or iv acyclovir
- Cytomegalovirus → ganciclovir or valganciclovir
- Oesophagitis in the immunocompromised that presents with punched-out ulcers → Herpes simplex virus-1
- Oesophagitis in the immunocompromised that presents with a white pseudomembrane → Candida spp.
- Oesophagitis in the immunocompromised that presents with linear ulcers → Cytomegalovirus

Candida oesophagitis

Although oropharyngeal candidiasis may be treated with topical antifungal agents (such as nystatin, clotrimazole, and amphotericin B oral suspension/lozenges) Candida oesophagitis requires oral or IV therapy (usually with fluconazole or itraconazole for at least 14-21 days).

HIV patient presented with painfull swallowing difficulty, an upper GI endoscopy shows ulcerative oesophagitis, what is the most likely diagnosis?



Eosinophilic oesophagitis

Overview

- Chronic immune-mediated eosinophil-predominant inflammation of the esophageal mucosa Should be considered in adults wit:
 - ⇒ History of food impaction, with persistent dysphagia, or
 - ⇒ Gastroesophageal reflux disease that fails to respond to medical therapy.
- Associated with Allergies : (e.g., asthma, rhinitis, atopic dermatitis, alimentary allergies)

Features

• Episodic oesophageal spasm and intermittent dysphagia

Diagnosis

Upper endoscopy with esophageal biopsy → presence of epithelial infiltrate of ≥ 15 eosinophils per high-power microscopy field

Treatment

- Diet modification. Refer for allergy testing (Eosinophilic esophagitis commonly associated with allergies). Once an antigen is identified, avoidance can improve symptoms
- Proton pump inhibitors. If the patient does not respond to a low-dose proton pump inhibitor, it is appropriate to increase the dose to a maximal dose before trying other treatment strategies.
- Topical "swallowed" corticosteroids for 8 weeks

Patients who present with food impaction, dysphagia, and history of atopy should undergo an upper endoscopy evaluation with esophageal biopsy to diagnose eosinophilic esophagitis.

Oesophageal cancer

Oesophageal adenocarcinoma is associated with GORD or Barrett's

Epidemiology

- Sex: ♂ > ♀ (3:1)
- Squamous cell carcinoma (SCC) is the most common type of esophageal cancer worldwide.
- Adenocarcinoma: most common type of esophageal cancer in the UK and US

Types

- Adenocarcinoma
 - ⇒ The most common form of esophageal cancer in the UK and US.
 - ⇒ Affects primarily white men.
 - ⇒ begins in the cells of mucus-secreting glands (glandular cells of the submucosa) in the esophagus.
 - ⇒ Occurs most often in the **lower** portion of the esophagus.
- Squamous cell carcinoma (SCC)
 - ⇒ The most prevalent esophageal cancer worldwide.
 - Develops in the thin, flat cells of the mucosa, which line the oesophagus.
 - ⇒ Occurs most often in the upper two-thirds of the esophagus.

Risk factors

- Risk factors for SCC
 - ⇒ Smoking
 - ⇒ Alcohol (Unlike adenocarcinoma).
 - ⇒ Diet
 - Red meat consumption
 - Low selenium levels. selenium supplementation reduces the risk
 - Zinc deficiency
 - Low dietary folate intake
 - low intake of fruits and vegetables
 - Hot liquids
 - ➡ Tylosis (rare, autosomal dominant disorder characterized by hyperkeratosis of the palms and soles, with thickening and fissuring of the skin.)
 - ⇒ **Achalasia** cardia
 - **⇒ Plummer-Vinson syndrome**
 - ⇒ Oral bisphosphonates
 - ⇒ Poor oral hygiene
 - ⇒ Infection with the human papillomavirus (HPV)

· Risk factors for adenocarcinoma

- ⇒ Gastroesophageal reflux (GORD) → the most common predisposing factor
- ⇒ Barrett esophagus
- ⇒ Smoking (twofold risk)
- ⇒ Obesity
- ⇒ Male sex
- ⇒ Older age (50–60 years)

Oesophageal cancer risk factors

- Alcohol is NOT a risk factor for Adenocarcinoma
- H. pylori infection associated with DECREASE incidence of oesophageal cancer.
 Helicobacter pylori may actually be protective against oesophageal cancer

The most important risk factors for esophageal adenocarcinoma are gastroesophageal reflux and associated Barrett esophagus.

The primary risk factors for squamous cell esophageal cancer are alcohol consumption, smoking, and dietary factors (e.g., diet low in fruits and vegetables).

Dermatological conditions associated with oesophageal carcinoma \rightarrow Tylosis (95% will get squamous oesophageal cancer)

Localization

- Squamous cell esophageal cancer: mostly in the upper two-thirds of the esophagus
- Adenocarcinoma: mostly in the lower third of the esophagus

Features

- Early stages: Often asymptomatic
- Late stage: progressive dysphagia, initially worse on solids and then later to include liquids
- Sudden onset of hiccups is common when tumor spreads to diaphragm
- · General signs: Weight loss, dyspepsia, anaemia

Diagnosis

- Upper GI endoscopy is the first line test
- Staging:
 - ⇒ For local tumor extent (mural invasion or tumour depth): Endoscopic ultrasound.
 - ⇒ For distant metastases:
 - CT of the Chest, abdomen and pelvis.
 - PET/CT scan is more sensitive than CT for detecting metastatic disease and are now widely used for detecting occult metastases if metastases are not seen on the initial staging CT scans.

Treatment

- Superficial intramucosal oesophageal cancer is best managed by endoscopic resection and surveillance.
- Early-stage cancers in surgical candidates are best treated by oesophagectomy.
- For locally advanced disease, combined modality therapy is considered the current standard. This involves chemotherapy or chemoradiotherapy followed by surgery.
- **High-risk patients** should be treated with a combination of chemotherapy and radiotherapy for best results, but local recurrence rates remain high.
- Palliative
 - ⇒ Opioid for pain relief
 - Nifedipine helps relieve painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve his odynophagia.

Oesophageal cancer

- Most oesophageal cancers are not resectable at presentation
- Chemo-radiotherapy then surgery is preferred to surgery alone.

What is the most common type of Oesophageal cancer?

- Squamous cell carcinoma is the most prevalent esophageal cancer worldwide.
- Adenocarcinoma is the most common form of esophageal cancer in the UK and United States

	Squamous cell carcinoma (SCC)	Adenocarcinoma
Prevalence	More common worldwide	More common in UK/US
Major risk factors	Smoking, alcohol Achalasia, Plummer Vinson	Barrett's oesophagus, GORD, smoking, and obesity.

Part of oesophagus affected	Upper 2/3	Lower 1/3
Prognosis	Poor long -term prognosis after resection	Better long-term prognosis after resection than that of SCC
Treatment	More sensitive to chemo-radio therapy than adenocarcinoma	

Prognosis

- Poor prognosis due to advanced disease at presentation.
- Most patients present with stage 3 disease (late stage) and survival at 5 years is only 9%.

Pharyngeal pouch

Definition

- A pharyngeal pouch is a **posteromedial** diverticulum through **Killian's dehiscence**.
 - ➡ Killian's dehiscence is a triangular area in the wall of the pharynx between the thyropharyngeus and cricopharyngeus muscles.
- Upper esophageal diverticulum (Common site)
- Zenker's diverticulum is the most common type of esophageal diverticula defined as a
 posterior "false" diverticulum that has a neck proximal to the cricopharyngeal muscle.

Epidemiology

- more common in older patients
- 5 times more common in men

Associations

- Achalasia → Inadequate relaxation of the esophageal sphincter ↑intraluminal pressure → outpouching of the esophageal wall → pulsion diverticulum (e.g., Zenker diverticulum)
- Inflammation of the mediastinum with scarring and retraction (e.g., secondary to tuberculosis or fungal infection) → traction diverticulum (Common site: the middle esophagus)
- · Gastro-oesophageal reflux disease

Features

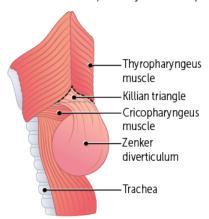
- Dysphagia (most common)
- · Regurgitation of undigested food
- Aspiration
- Coughing after food intake
- Retrosternal pressure sensation and pain
- Halitosis (a bad breath)
- Neck swelling which gurgles on palpation (Boyce's sign)
- Weight loss

Diagnosis

- Barium studies (best confirmatory test)
 - detected best by using lateral X-ray shows a contrast-filled pouch protruding dorsally from the hypopharynx at the level of C5/C6
 - ⇒ Upper gastrointestinal endoscopy is risky, since the pouches are thin-walled and easy to perforate; this is the reason why a barium swallow may be the preferable first-line investigation in elderly patients with dysphagia.
- Upper endoscopy under direct vision should be performed to exclude malignancy.

Treatment

- Diverticula of the **upper** esophagus :Surgical, with either an open or endoscopic approach.
- Diverticula of the **middle and distal** esophagus (traction diverticula and epiphrenic diverticula) usually do not require treatment (most of them are asymptomatic).



Acute upper gastrointestinal bleeding (UGIB) (NICE 2012)

Definition

• bleeding derived from a source proximal to the ligament of Treitz.

Causes: Most commonly due to either:

- · peptic ulcer disease or
- oesophageal varices.

Risk assessment

- · use the Blatchford score at first assessment, and
- the full Rockall score after endoscopy

Blatchford score

- The **Blatchford score** is based on clinical parameters alone:
 - ⇒ Elevated blood urea nitrogen
 - ⇒ Reduced haemoglobin
 - ⇒ A drop in systolic blood pressure
 - ⇒ Raised pulse rate
 - ⇒ The presence of melaena or syncope, and
 - ⇒ Evidence of hepatic or cardiac disease.

Admission risk marker	Score	
Urea (mmol/l)	6.5 - 8 = 2 8 - 10 = 3 10 - 25 = 4 > 25 = 6	
Haemoglobin (g/l)	Men • 12 - 13 = 1 • 10 - 12 = 3 • < 10 = 6 Women	

Admission risk marker	Score	
	10 - 12 = 1< 10 = 6	
Systolic blood pressure (mmHg)	100 - 109 = 1 90 - 99 = 2 < 90 = 3	
Other markers	Pulse >=100/min = 1 Presentation with melaena = 1 Presentation with syncope = 2 Hepatic disease = 2 Cardiac failure = 2	

Patients with a Blatchford score of 0 may be considered for early discharge

Rockall score

- Used to:
- determine the prognosis of upper GIT bleeds.
- > assess severity of GIT bleeds and / or to triage patients for emergency endoscopy.
- Consists of 5 categories:
- 1. age
- 2. shock
- 3. co-morbidity e.g. ischaemic heart disease (IHD)
- 4. diagnosis and
- 5. evidence of bleeding (the latter two can only be categorised after endoscopy).
- ⇒ Each category is scored between 0 and 2 points, with the exception of co-morbidities which has a maximum score of 3.
- ➡ Renal failure, liver failure and metastatic cancer carry the highest points, and thus confer the highest risk of death, of any of the other parameters included in the scoring system.

• The full Rockall scoring system is shown in the table below:

	Score 0	Score 1	Score 2	Score 3
Age	<60	60-79	>80	-
Shock	No shock	Pulse >100	Systolic blood pressure <100 mmHg	-
Co-morbidity	Nil major		CCF, IHD, major morbidity	Renal or liver failure, metastatic cancer
Diagnosis	Mallory- Weiss tear	All other diagnoses	GI malignancy	-
Evidence of bleeding	None	-	Blood, adherent clot, spurting vessel	-

- Interpretation:
 - Increasing scores are strongly correlated with increasing risk of mortality,
 - The total score predicts mortality as follows:

- **❖** Score 0, **→** 0.2%;
- \star score 2, \rightarrow 5%;
- score 4, → 24%;
- \star score 6, \rightarrow 49%.
- > correlation with **risk of re-bleeding** is also present but not as strong.

Grades of hypovolaemic shock

The table below outlines the signs and symptoms of the different grades of hypovolaemic shock:

Grade 1	 Up to about 15% loss of effective blood volume (~750ml in an average adult who is assumed to have a blood volume of 5 litres). This leads to a mild resting tachycardia and can be well tolerated in otherwise healthy individuals. In the elderly or those with underlying conditions such as ischaemic heart disease the additional myocardial oxygen demands may not be tolerated so well.
Grade 2	 Between 15-30% loss of blood volume (750-1500ml) will provoke a moderate tachycardia and begin to narrow the pulse pressure. The capillary refill time will be extended.
Grade 3	 At 30 - 40% loss of effective blood volume (1500 - 2000 ml) the compensatory mechanisms begin to fail and hypotension, tachycardia and low urine output (<0.5ml/kg/hr in adults) are seen.
Grade 4	 At 40-50% loss of blood volume (2000-2500 ml) profound hypotension will develop and if prolonged will cause end-organ damage and death.

Classification of haemorrhage:

Parameter	1	П	III	IV
Blood loss (ml)	<750	750-1500	1500-2000	>2000
Blood loss (%)	<15%	15-30%	30-40%	>40%
Pulse rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14-20	20-30	30-40	>35
Urine output (ml/hour)	>30	20-30	5-15	Negligible
CNS symptoms	Normal	Anxious	Confused	Lethargic

Blood test evidence of upper gastrointestinal haemorrhage

- Reactive thrombocytosis
- Urea elevated in excess of creatinine

Treatment

Resuscitation

- > ABC, wide-bore intravenous access
- ▶ platelet transfusion if actively bleeding platelet count of less than 50 x 10*9/litre
- fresh frozen plasma to patients who have either a fibrinogen level of less than 1 g/litre, or a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal
- prothrombin complex concentrate to patients who are taking warfarin and actively bleeding

Endoscopy

- > should be offered immediately after resuscitation in patients with a severe bleed
- > all patients should have endoscopy within 24 hours
- Recent NICE guidelines do not recommend proton pump inhibition (PPIs) before endoscopy.
- He may have alcohol dependency and therefore should be prescribed Pabrinex whilst waiting for endoscopy.

Management of non-variceal bleeding

- NICE do not recommend the use of proton pump inhibitors (PPIs) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding although PPIs should be given to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy
- ➤ The best evidence for pharmacological intervention post-stabilisation of bleeding peptic ulcer disease is for proton pump inhibitors.
 - the most appropriate intervention to prevent further bleeding → IV omeprazole
 - reduction in risk of recurrent bleeding of over 50%.
 - * reduction in need for surgical intervention of approximately 40%.
- if further bleeding then options include repeat endoscopy, interventional radiology and surgery

Management of variceal bleeding

- ⇒ **terlipressin** and prophylactic antibiotics should be given to patients at presentation (i.e. before endoscopy)
- ⇒ band ligation should be used for oesophageal varices and injections of N-butyl-2cyanoacrylate for patients with gastric varices
- ⇒ transjugular intrahepatic portosystemic shunts (TIPS) should be offered if bleeding from varices is not controlled with the above measures

Oesophageal varices

Antibiotic prophylaxis reduces mortality in cirrhotic patients with gastrointestinal bleeding

Overview

- Oesophageal varices are tributaries of the left gastric vein , found in lower 1/3 of esophagus
 - ⇒ **lower 1/3 of oesophagus** is drained into the superficial veins lining the esophageal mucosa, → **left gastric vein** → portal vein.
 - ⇒ upper 2/3 of oesophagus are drained via esophageal veins → azygos vein
 → superior vena cava. (These veins have no part in the development of esophageal varices)
- Esophageal varices are the most common cause of death in cirrhosis.

Acute treatment of variceal haemorrhage

Terlipressin - method of action = constriction of the splanchnic vessels

- ABC: patients should ideally be resuscitated prior to endoscopy
- · correct clotting: FFP, vitamin K
- · vasoactive agents:
 - ⇒ terlipressin is currently the only licensed vasoactive agent and is supported by NICE guidelines.
 - powerful splanchnic vasoconstrictor
 - It has been shown to be of benefit in initial haemostasis and preventing rebleeding.
 - the most appropriate treatment whilst awaiting urgent endoscopy
 - As a vasoconstrictor its administration is contraindicated in those with a history of ischaemic heart disease as it may precipitate myocardial ischaemia
 - ⇒ Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality
- prophylactic antibiotics
 - ⇒ have been shown in multiple meta-analyses to reduce mortality in patients with liver cirrhosis.
 - ⇒ Quinolones are typically used.
- endoscopy:
 - endoscopic variceal band ligation is superior to endoscopic sclerotherapy. NICE recommend band ligation
- Sengstaken-Blakemore tube if uncontrolled haemorrhage
 - Balloon tamponade (for example, using a Sengstaken-Blakemore tube) may be used as a holding measure in situations where, for whatever reason, a definitive procedure cannot be performed to control bleeding (for example, endoscopy or transjugular intrahepatic portosystemic shunting).
 - ⇒ It is generally very effective in achieving control of variceal bleeding.
- Transjugular Intrahepatic Portosystemic Shunt (TIPSS) if above measures fail

Prophylaxis of variceal haemorrhage

- propranolol:
 - ⇒ reduced rebleeding and mortality compared to placebo
- endoscopic variceal band ligation (EVL)
 - ⇒ is superior to endoscopic sclerotherapy.
 - ⇒ It should be performed at two-weekly intervals until all varices have been eradicated.
 - ⇒ Proton pump inhibitor cover is given to prevent EVL-induced ulceration

Prognosis

Overall mortality from bleeding varices is around 30%

Esophageal Rupture

- Causes
 - ⇒ latrogenic esophageal perforation:
 - most common cause of esophageal perforation
 - Generally injury during upper endoscopy
 - Symptoms usually within 24 hours of endoscopy
 - ⇒ Foreign body ingestion
 - ⇒ Trauma
 - ⇒ Malignancy
 - ⇒ Boerhaave syndrome

- Severe vomiting/increased intrathoracic pressure → rupture of all layers of the esophageal wall
- In > 90% of cases, the rupture occurs in the distal third of the esophagus on the left dorsolateral wall surface.
- Sex: ♂ > ♀ (3:1)
- Associations
 - Excessive intake of alcohol or food in the recent past
 - Repeated episodes of vomiting
 - Childbirth
 - Seizures
 - Prolonged coughing
 - Weightlifting

Feature:

- Mackler's triad (vomiting, chest pain and surgical emphysema) is classical but absent in almost half the cases.
 - surgical emphysema
 - ❖ Subcutaneous emphysema → crepitus in the suprasternal notch
 - mediastinal emphysema → "crunching" or "crackling" sound on chest auscultation (Hamman's sign)
 - The most relevant finding on examination is the crepitus over the chest
- Dyspnea, cyanosis

investigations:

- Gastrografin swallow will confirm the site of perforation in approximately 65-75% of cases, and is the recommended first line investigation.
- chest x ray
 - useful in the initial diagnosis
 - The most common finding is a **unilateral effusion**, usually on the left.
 - Because the most perforations occur in the left posterior aspect of the esophagus.
 - Other findings may include
 - pneumothorax, hydropneumothorax, pneumomediastinum,
 - surgical emphysema.
 - mediastinal widening.

Lateral neck x rays

 may be useful in the early stages where the diagnosis is uncertain and surgical emphysema is not seen on a plain CXR.

> CT scan:

- indicated in unstable/uncooperative patients, pneumoperitoneum on x-ray, or ifx-rays and contrast esophagram are inconclusive
- Barium swallow
 - more sensitive at 90% for detecting small perforations but carries the risk of a severe inflammatory response (mediastinaitis).

Prognosis

- A reported mortality estimate is approximately 35%, making it the most lethal perforation of the GI tract.
- if intervention is delayed longer than 24 hours, the mortality rate (even with surgical intervention) rises to higher than 50% and to nearly 90% after 48 hours. Left untreated, the mortality rate is close to 100%.

Hiccup

- caused by frequent or rhythmic clonic contraction of the diaphragm.
- When prolonged, other causes should be considered including:
 - > CNS disease posterior fossa tumour, brain injury, encephalitis
 - Phrenic nerve or diaphragm irritation tumour, pleurisy, pneumonia, intrathoracic adenopathy, pericarditis, gastro-oesophageal reflux, oesophagitis
 - Systemic causes include alcohol intoxication and uraemia.
 - > Other causes include foreign body or insect in the ear.
 - In infants it may be associated with appose or hyperventilation.
- Treatment
 - ⇒ Folk remedies include aerophagia, breath holding, pharyngeal stimulation, distraction.
 - ⇒ Haloperidol, metaclopramide and several anaesthetic agents are also said to work.

Gastric conditions

Helicobacter pylori

H. pylori eradication:

- · PPI + amoxicillin + clarithromycin, or
- PPI + metronidazole + clarithromycin

Overview

 Helicobacter pylori is a Gram negative bacteria associated with a variety of gastrointestinal problems, principally peptic ulcer disease

Associations

- Peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers)
- gastric cancer (≈ 5%)
 - ⇒ The most common location is the **lesser curvature**.
 - ⇒ appears as an ulcer with heaped-up margins.
- B cell lymphoma of MALT tissue (eradication of H pylori results causes regression in 80% of patients)
- Atrophic gastritis

Helicobacter pylori is NOT associated with GORD

- The is no apparent role of H pylori in Gastro-oesophageal reflux disease (GORD)
- there is currently no role in GORD for the eradication of H pylori

Diagnosis

Urea breath test - no antibiotics in past 4 weeks, no antisecretory drugs (e.g. PPI) in past 2 weeks

Noninvasive methods

Urea breath test

- · The preferred method for initial diagnosis or confirmation of eradication
- sensitivity 95-98%, specificity 97-98%
- should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a proton pump inhibitor)

Serum antibody

- sensitivity 85%, specificity 80%
- remains positive after eradication (cannot distinguish between a past and current infection.)

Stool antigen test

- Sensitivity 90%, specificity 95%
- Can be used for initial diagnosis BUT NICE guidelines do not recommend its use to confirm eradication due to a lack of evidence.

Invasive methods

Rapid urease test (e.g. CLO test)

- · Performed on biopsy tissue obtained during endoscopy
- Detects the amount of ammonia produced by H. pylori during urea hydrolysis
- Sensitivity 93-97%, specificity 95-98%
- the false negative rate increases significantly in:
 - ⇒ recent gastrointestinal haemorrhage,
 - ⇒ acid suppression therapy and
 - ⇒ recent antibiotic treatment.

Culture of gastric biopsy (Gold standard)

- sensitivity 70%, specificity 100%
- Staining and direct microscopic identification (silver stain)
- Curved, gram-negative rods with multiple flagella is the typical appearance of H.pylori.

Gastric biopsy

- · Histological evaluation alone, no culture
- Sensitivity 95-99%, specificity 95-99%

Test to confirm eradication:

- When to test for complete eradication?
 - ⇒ Re-testing for *Helicobacter pylori* is **indicated only in the setting of peptic ulcer** disease to confirm eradication where an initial test is positive.
- Which test?
 - Carbon-13 urea breath testing is the <u>only</u> well validated method for confirming the successful eradication of *Helicobacter pylori*.

PPIs should be discontinued at least 2 weeks prior to most H. pylori testing modalities to minimize rates of false-negative results. However, some testing modalities, e.g., histology, are not affected by recent PPI treatment.

Management

- First-line treatment
 - ⇒ Not allergic to penicillin → PPI + amoxicillin + either clarithromycin or metronidazole.
 - \Rightarrow Allergic to penicillin \rightarrow PPI + metronidazole + clarithromycin
 - ⇒ Allergic to penicillin + previous exposure to clarithromycin → PPI + bismuth + metronidazole + tetracycline

- Re-testing for *H. pylori*
 - ➡ Re-testing for *H. pylori* before second-line treatment is considered to confirm eradication as there are serious side effects associated with antibiotics, e.g. *Clostridium difficile* infection, and antibiotic resistance is increasing.
 - ⇒ Eradication therapy is effective in 80-85% of cases and should not be repeated without evidence of treatment failure.
 - the carbon-13 urea breath test is the most accurate method of re-testing for H. pylori.
 - ⇒ NICE guidelines 2019 state: Perform re-testing for H pylori using a carbon-13 urea breath test. (There is currently insufficient evidence to recommend the stool antigen test as a test of eradication)
- Second-line treatment (If still symptomatic after first-line + positive re-testing for H. pylori)
 - ⇒ Not allergic to penicillin → PPI + amoxicillin + either clarithromycin or metronidazole (whichever was not used first-line)
 - ⇒ If there is a previous exposure to clarithromycin and metronidazole →PPI + amoxicillin + quinolone or tetracycline (whichever has the lowest acquisition cost).
 - ⇒ Allergic to penicillin + NO previous exposure to a quinolone → PPI + metronidazole + levofloxacin
 - ⇒ Allergic to penicillin + previous exposure to a quinolone → PPI + bismuth + metronidazole + tetracycline.

Peptic ulcer

Basic

Bleeding from Posterior duodenal ulcers are due to erosion of the gastroduodenal artery

- The right and left gastroepiploic arteries (gastro-omental arteries) supply the greater curvature of the stomach.
 - ➤ The source of ulcer bleeding in the greater curvature of the stomach → Left gastroepiploic artery
- The right gastric artery arises from the hepatic artery or the left hepatic artery, supplies
 the pylorus and travels along the lesser curvature of the stomach, supplying it, and
 anastomosing with the left gastric artery.
 - ➤ the cause of ulcer bleeding in the lesser curvature of the stomach → right gastric artery
- The **pancreaticoduodenal artery** (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum and the head of the pancreas.
- The **right hepatic artery** supplies the right lobe of the liver and part of the caudate lobe.

The golden notes

Sources of bleeding in peptic ulcers:

- greater curvature of the stomach → Left gastroepiploic artery
- lesser curvature of the stomach → right gastric artery
- Posterior duodenal ulcers → gastroduodenal artery
 - pancreaticoduodenal artery (a branch of the gastroduodenal artery) supplies mainly the upper and lower duodenum.

The golden notes

Sites of peptic ulcers:

- 80% are duodenal.
- The most common site → near the pylorus, on the duodenal side
- The less frequent site → lesser curvature of stomach or at the point at which the esophagus enters the stomach.

Risk factors for peptic ulceration include

- Helicobacter pylori (H. pylori) infection,
- non-steroidal anti-inflammatory drug (NSAID) use,
- · cigarette smoking and
- genetic factors Lewis blood group antigens facilitate *H. pylori* attachment to the mucosa.

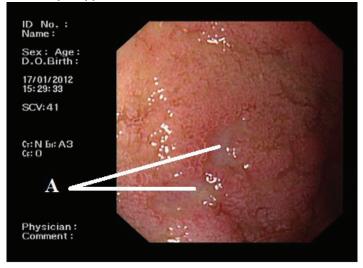
Interventions for peptic ulcer disease (NICE 2012)

- peptic ulcer + H pylori → H pylori eradication therapy
- peptic ulcer + H pylori → retesting for H pylori 6 to 8 weeks after beginning treatment,
- gastric ulcer + H pylori → repeat endoscopy 6 to 8 weeks after beginning treatment
- In people at high risk (previous ulceration) and for whom NSAID continuation is necessary, consider a COX-2 selective NSAID instead of a standard NSAID with a PPI.
 - ⇒ The Two highly selective or specific in their ability to inhibit COX-2 while having little or no COX-1 affinity are rofe**coxib** and cele**coxib**.
- Offer H₂RA therapy if there is an inadequate response to a PPI.

The effect of Helicobacter eradication on healing and recurrence of peptic ulcer:

- The effects is dependent upon whether ulceration is gastric or duodenal and whether the
 patient is taking non-steroidal anti-inflammatory drugs or not.
 - For duodenal ulcers eradication slightly increases healing (additional 5.4% over acid suppression alone) but dramatically decreases recurrence (increases the number of patients ulcer free at 12 months by 52%).
 - For gastric ulcers eradication therapy has no effect on healing but does decrease recurrence (an additional 32% of patients are ulcer free at 12 months compared to acid suppression alone).
 - In patients taking non-steroidal anti-inflammatory drugs eradication therapy has no effect on peptic ulcer healing (gastric or duodenal), but will decrease ulcer recurrence
 - continued non-steroidal anti-inflammatory drug use markedly reduces the size of effect that eradication therapy has on reducing ulcer recurrence.

Endoscopic appearance of ulcers:



- The endoscopic appearances are of two small duodenal ulcers (A) without evidence of recent haemorrhage. There is some co-existent duodenitis.
- The presence of villi identifies this as the duodenum.
- The mucosal appearances are not consistent with that of the stomach (absence of rugae, paler squamous epithelium rather than redder columnar epithelium) or the oesophagus (pale pink non-villous squamous epithelium).

Following endoscopic intervention

- immediately post-endoscopy, patients should be commenced on a high dose oral or intravenous proton pump inhibitor, this reduces the risk of rebleeding.
- Amoxicillin and clarithromycin may be indicated if there is evidence of Helicobacter pylori infection. This need not be started immediately post-endoscopy but treatment should not be unnecessarily delayed.

Zollinger-Ellison syndrome

Zollinger-Ellison syndrome: epigastric pain and diarrhoea

Definition

- gastrinoma (Zollinger-Ellison syndrome) is a gastrin-secreting neuroendocrine tumor that is most often localized to the duodenum and pancreas.
 - > Gastrin is released by G cells in the antrum under normal physiological conditions.

Tumor location

- Duodenum (~ 70% of cases)
 - Most ulcers are located in the first part of the duodenum.
- Pancreas (~ 25% of cases): typically, the head
- Ectopic locations (5–15% of cases)

Causes

- Most gastrinomas occur sporadically.
- Around 30% occur as part of MEN type I syndrome

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Age of onset: 30-50 years

Pathophysiology

- Hypergastrinemia → stimulation of parietal cells → gastric acid hypersecretion, which leads to:
 - Peptic ulcer disease
 - ➤ Inactivation of pancreatic enzymes → diarrhea, steatorrhea → malabsorption

Features

- multiple gastroduodenal ulcers
- diarrhoea
 - diarrhea in Zollinger-Ellison syndrome (gastrinoma) is due to malabsorption.
- malabsorption

Diagnosis

- Best initial test: esophagogastroduodenoscopy
 - Important to rule out *H. pylori* infection and malignant ulcers
 - > Typically reveals multiple ulcers and thick gastric folds
 - ➤ ↓ Gastric pH
- Fasting gastrin levels: the single best screen test
 - ⇒ fasting gastrin test > 1000 with low PH < 2 is diagnostic
 - ⇒ if level < 1000 and the diagnosis is suspected, then secretin stimulation testing or calcium stimulation testing</p>
 - secretin stimulation test
 - ❖ rise > 200 after 15 minute of dosing is considered positive
 - calcium stimulation test
 - ❖ rise > 395 is considered positive
- Secretin stimulation test (if fasting serum gastrin test is inconclusive)
 - ⇒ gastrin levels remaining elevated after administration of secretin.

The presence of multiple, large (> 2 cm) ulcers in atypical locations (e.g., the **jejunum**) should raise suspicion of gastrinoma.

Treatment

- Reduce acid production
 - > **PPIs** (e.g., omeprazole), H2 antagonists (e.g., ranitidine)
 - > Octreotide (a somatostatin analog) may be used in refractory cases.
- Non-metastatic disease:
 - ⇒ surgical resection of the gastrinoma is the treatment of choice
 - possibility of cure is up to 25% of patients.
- Metastatic disease:
 - ⇒ chemotherapy
 - □ In approximately 50% of cases, the tumor has already metastasized at the time of diagnosis

Somatostatin

Source	Action	Regulation	Notes
 D cells (pyloric antrum, and duodenum mucosa) delta cells (pancreas) ventromedial nucleus of the hypothalamus. 	 ↓ gastric H⁺ and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release ↓ GH release 	↑ by H ⁺ ↓ by vagal stimulation	 Inhibitory hormone Antigrowth hormone effects (digestion and absorption of substances needed for growth) Produce vasoconstriction of the splanchnic system. Somatostatin is treatment for VIPoma and carcinoid tumors

- · Inhibit TSH secretion.
- Mechanism of action
 - Somatostatin receptor is linked to adenylyl cyclase by <u>Gi</u> protein, which inhibits cAMP production and reduces secretion of hormones.

Somatostatinoma

- Annual incidence → 1 in 40 million.
- Associations:
 - ⇒ Impaired glucose tolerance (IGT) or diabetes mellitus (95%)
 - ⇒ Gallstones (68%)
 - ⇒ Weight loss (25%)

- ⇒ Anaemia (14%)
- ⇒ Multiple endocrine neoplasia type 1
 (7%)
- ⇒ Diarrhoea

- Diagnosis:
 - ⇒ The tumours are often multisecretory → ↑↑ Somatostatin, adrenocorticotropic hormone (ACTH) and calcitonin
 - ⇒ Contrast spiral computed tomography scanning is effective for detecting the primary tumour in only 50% of cases;
 - Radiolabeled octreotide or endoscopic ultrasound scanning are often be required.
- Treatment:
 - ⇒ surgery is rarely possible due to presence of metastases,
 - ⇒ hepatic embolisation can be helpful for symptom control.

Gastric MALT lymphoma

Gastric MALT lymphoma - eradicate H. pylori

Overview

- lymphoma of Mucosa-Associated Lymphoid Tissue (MALT)
- (MALT) is typically a low-grade, B-cell neoplasia originating from mucosa-associated lymphoid tissue
- associated with *H. pylori* infection in 95% of cases
- good prognosis
- Within the stomach the antrum is most commonly involved

Epidemiology

MALT lymphoma

- ⇒ 7% to 8% of all B-cell lymphomas
- ⇒ the third most common type of non-Hodgkin's lymphoma
- ⇒ the most common type of primary **extra-nodal** lymphoma and represents up to 50% of primary gastric lymphomas.
- Gastric MALT lymphomas
 - ⇒ account for about 30% of all MALT lymphomas,
 - ⇒ median age of 57 years
 - ⇒ no sex predilection.

Features

- paraproteinaemia may be present
- infiltrate of small-size lymphocytes that destroy gastric glands, configuring the so-called 'lymphoepithelial lesion' which is pathognomonic of lymphoma
- The common cytogenetic abnormalities demonstrated in MALT lymphomas is t(11;18),
 - ⇒ seen in 30% to 40% of gastric and lung MALT lymphomas
 - ⇒ This is clinically important, as t(11;18)-positive cases are less likely to respond to H pylori-eradication therapy
 - ⇒ there is a high incidence of t(11;18) in *H pylori*-negative gastric MALT lymphoma,
 - ⇒ t(11;18)-positive cases are more likely to present with advanced-stage disease associated with aberrant expression of nuclear BCL10
 - ⇒ t(11;18)-positive cases are **less likely to transform to aggressive lymphomas**, as they are unlikely to develop secondary chromosomal abnormalities.

Treatment

- if low grade then 80% respond to *H. pylori* eradication
- low grade localised gastric helicobacter pylori positive :
 - ⇒ first line → antibiotics plus a proton-pump inhibitor (PPI)
 - ⇒ second line → radiotherapy
 - Patients are considered to have failed *H pylori* eradication when:
 - there is no regression at repeat endoscopy 2 months after treatment,
 - or when there is lack of complete regression at approximately 18 months after treatment.
- low grade localised gastric helicobacter pylori negative:
 - ⇒ first line → radiotherapy
- low grade advance gastric (Disease not confined to the stomach)
 - ⇒ first line → chemotherapy
 - If *H pylori* -positive, → add eradication therapy.
- High grade histological transformation:
 - ⇒ First line → chemotherapy
 - ⇒ MALT lymphoma is defined as a low-grade neoplasm. However, gastric MALT lymphoma can show a component of high-grade transformation.
 - ⇒ This is characterised by an increase in the number of transformed blasts, which can eventually lead to complete effacement of the original MALT lymphoma.

Ref: bestpractice.bmj.com.2017

Gastroparesis

Definition

• Delayed gastric emptying in the absence of a mechanical obstruction

Causes

- Mostly idiopathic but also associated with diabetes mellitus and upper GI surgery
- Occurs in 10–20% of diabetics after 10 years.

Mechanism

• The major stimulant for gastric motility is "stretch."

 In patients with longstanding diabetes, there is impaired ability to perceive stretch in the GI tract and impaired motility.

Symptoms

- erratic blood glucose control
- · chronic nausea, vomiting, epigastric pain, bloating
- early satiety, abdominal fullness, constipation.

Diagnosis

- Gastric-emptying scan
 - ⇒ Gastric emptying scintigraphy demonstrating <u>>10% retention of the radionuclide</u> meal at the end of 4 hours is diagnostic.

Management

- Metoclopramide: the first drug of choice
 - o **Action:** both a dopamine receptor antagonist and a serotonin receptor agonist.
 - Indication: It is better for short-term treatment. Its use in the long-term treatment of gastroparesis is no longer recommended.
 - Side effects: extrapyramidal
- Domperidone
 - ⇒ Action: dopamine antagonist with an affinity for the D2 receptor in the brain and peripheral gastrointestinal system.
 - ⇒ **Indications:** only used for nausea and vomiting and is no longer recommended for the treatment of conditions such as heartburn, bloating, or stomach discomfort.
 - ➡ Side effects: associated with a small increased risk of life-threatening cardiac effects.
 - Advantages: It does not cross the blood-brain barrier, so does not cause the neurological adverse effects associated with metoclopramide.
 - ⇒ Contraindications
 - Contraindicated in patients with hepatic or cardiac disease.
 - Should not be administered with other drugs that prolong the QT interval or inhibit CYP3A4
- Erythromycin
 - ⇒ **Action:** ↑ release of "motilin," a pro-motility GI hormone.
 - ⇒ used in the acute care setting if the patient is admitted to hospital.
- Dietary modification (small, frequent meals that are low in fat and contain only soluble fiber), glycemic control and hydration

Type 2 diabetes with erratic blood glucose control or unexplained gastric bloating or vomiting \rightarrow Think about a diagnosis of gastroparesis.

Gastric cancer

Gastric adenocarcinoma - signet ring cells

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Peak incidence: 70 years
- Geographical distribution:
 - ⇒ strong regional differences
 - ⇒ High incidence in South Korea, China and Japan

- ⇒ Declining incidence in the United States and Europe
- overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- Adenocarcinoma is the most common gastric cancer (90% of cases). Arises from glandular cells in the stomach. Most commonly located on the lesser curvature

Risk factors

- **Exogenous risk factors**
 - ⇒ Diet: salty, spicy, nitrates, dietary nitrosamines (smoked foods).
 - ⇒ H. pylori infection: the most common risk factor (> 60%)
 - ⇒ Smokina
 - ⇒ Epstein-Barr virus
 - ⇒ Low socioeconomic status
 - ⇒ Obesity
- **Gastric conditions**
 - ⇒ Pernicious anaemia → Chronic atrophic gastritis → gastric adenocarcinoma.
 - ⇒ Achlorhydria: decrease in gastric acid production (e.g., due to Ménétrier disease)

 - ⇒ Partial gastrectomy
 - ⇒ Adenomatous gastric polyps
 - ⇒ Gastroesophageal reflux disease
- **Hereditary factors**
 - ⇒ Positive family history
 - ⇒ Blood type A: qAstric cAncer
 - ⇒ Gastric adenomatous polyps: Hereditary nonpolyposis colorectal cancer
- Factors associated with decreased risk of gastric tumours (negative association)
 - ⇒ Duodenal ulcer
 - ⇒ NSAID use

Features

- Early stages: Often asymptomatic
- About half of patients with gastric cancer present with advanced disease at the time of diagnosis.
- General signs: Weight loss, chronic iron deficiency anemia
- Signs of gastric outlet obstruction: Dysphagia, Abdominal pain, Early satiety, Vomiting
- Signs of upper gastrointestinal bleeding: Hematemesis, Melena
- Signs of metastatic disease
 - ⇒ Hepatomegaly, Ascites: liver is the most common site of metastasis.
 - ⇒ Left supraclavicular adenopathy (Virchow node)
 - ⇒ Palpable umbilical nodule (Sister Mary Joseph node)
 - ⇒ Mucin-secreting "signet-ring" cells in the ovaries are diagnostic of Krukenberg tumors, which are indicative of stomach adenocarcinoma metastasis.
- Paraneoplastic syndromes
 - ⇒ Leser-Trélat sign (: (multiple seborrheic keratoses, often with an inflammatory base.)
 - ⇒ Malignant acanthosis nigricans

Always rule out malignancy in patients with acanthosis nigricans.

Types of gastric adenocarcinoma

- · Intestinal type of gastric adenocarcinoma
 - ⇒ the **most common** type of gastric adenocarcinoma.
 - ⇒ presents as a large, **irregular ulcer with heaped up margins**, typically at the lesser curvature of the antrum.
 - ⇒ associated with Helicobacter pylori, chronic gastritis, atrophy, and intestinal metaplasia

Diffuse gastric adenocarcinoma

- ⇒ characterized by thickening and rigidity of the gastric wall.
- ⇒ Infiltrate the submucosa, (Scirrhous infiltration of the submucosa) so that mucosal sampling may not show neoplastic cells.
- ⇒ associated with a poor prognosis compared with the intestinal type
- ⇒ Unlike the intestinal type of gastric adenocarcinoma, it is more common in women and individuals less than 50 years old.
- ⇒ associated with H. pylori infection, **but NOT with atrophy and intestinal metaplasia**
- ⇒ associated with signet ring cells and linitis plastica.
- ➡ Linitis plastica is a particularly aggressive form of diffuse adenocarcinoma. It is also known as "leather bottle stomach" because the stomach is diffusely thickened, with a small lumen that cannot expand, leading to the symptom of early satiety. This thickening can be seen on the CT image.

Histology

- Signet ring cells may be seen in gastric cancer.
 - ⇒ They contain a large vacuole of mucin which displaces the nucleus to one side.
 - ⇒ Higher numbers of signet ring cells are associated with a worse prognosis

Diagnosis

- Endoscopy with biopsy: (best initial and confirmatory test)
- Staging: CT or endoscopic ultrasound endoscopic ultrasound has recently been shown to be superior to CT

Treatment

- Early-stage disease → surgery alone (**Total or sub-total Gastrectomy**)
- Locally advanced disease → surgery followed by postoperative chemoradiation, or chemotherapy before and after surgery.
- Metastatic disease → chemotherapy, immunotherapy, or chemoradiation and supportive care measures.
- Trastuzumab is indicated for HER2-positive gastric adenocarcinomas.

Trastuzumab is indicated for HER2-positive gastric adenocarcinomas.

(TRUSTuzumab; HER2; Gastric cancer; Breast cancer)

Post gastrectomy complications

- Malabsorption: Lack of chyme stimulation → ↓ pancreatic enzyme levels → protein and carbohydrate maldigestion → fat-soluble vitamin deficiency
- Loss of parietal cells → ↓/absent intrinsic factor production → vitamin B12 deficiency → pernicious anemia

- Loss of parietal cells → ↓ gastric acid → ↓ iron absorption → iron deficiency anemia (low pH environment is necessary for the reduction of Fe³⁺ (ferric iron) to Fe²⁺ (ferrous iron) the absorbable form of iron).
- Small intestinal bacterial overgrowth
- Dumping syndrome
 - ⇒ **Early dumping** (Occur hours after meal ingestion): rapid emptying of undiluted hyperosmolar chyme into the small intestine → fluid shift to the intestinal lumen → small bowel distention → vagal stimulation → increased intestinal motility (nausea, vomiting, diarrhoea, and cramps) + Vasomotor symptoms such as sweating, flushing, and palpitations.
 - ⇒ Late dumping (occur hours after meal ingestion): rapid emptying of glucosecontaining chyme into the small intestine → quick reabsorption of glucose → hyperglycaemia → excessive release of insulin → hypoglycaemia and release of catecholamines → signs of hypoglycaemia (e.g., hunger, tremor, light-headedness)

Prognosis

- At diagnosis, 60% of cancers have already reached an advanced stage that does not allow for curative treatment.
- 5-year survival
 - ⇒ confined to the mucosa and submucosa (> 90%)
 - ⇒ extended beyond the submucosa (<10%).

Gastrointestinal stromal tumour (GIST)

- common type of sarcoma; it develops in the gastrointestinal (GI) tract
- occur most often in adults over the age of 50 years
- Location of GISTs:
 - ⇒ most commonly involve the stomach (60%),
 - ⇒ jejunum and ileum (30%),
 - ⇒ duodenum (4%–5%), and
 - ⇒ colorectal (< 5%).
- Tumours in the small bowel and rectum appear to be more aggressive than those occurring in the stomach.
- the cell of origin of gastric GISTs → Interstitial cells of Cajal within Auerbach's plexus
 - the interstitial cells of Cajal act as pacemaker cells of the GIT, with regulation of peristalsis in the adult intestine
- Approximately 80%–95% of GISTs harbor an activating mutation in the KIT gene
 - ⇒ about 80% of KIT-negative GISTs have an activating mutation in the PDGFRA gene.
 - a mutation in PDGFRA may make the tumour resistant to the standard drugs to treat GIST.
 - tumours with a PDGFRA mutation are usually less aggressive than the more common ones with KIT mutation.
- 50% are present with metastatic disease, (commonly liver metastases),
- Features
 - Mostly asymptomatic.
 - > Tumor induce GI bleed and anemia
 - > Other symptoms secondry to mass effects:
 - > Abdominal discomfort, early satiety, palpable abdominal mass
 - > Bowel obstruction or perforation
 - Dysphagia
- Diagnosis:
 - Gold standard test is endoscopy with biopsy
 - Histopathology: Spindle cell in 70 to 80%, epitheliods cells in 20 to 30

- CT and endoscopic ultrasound allow tumour staging to plan further management.
- Immunohistochemical Stainning
 - Up to 95% of GISTs are positive for KIT expression (CD117)
 - 60%–70% are positive for CD34 expression.
- Management
 - all GISTs ≥ 2 cm → surgery
 - Surgery is usually the first treatment method used for GIST.
 - If the tumour is too large to be removed at the time of diagnosis, it may be treated initially with imatinib. If sufficient shrinkage has occurred after 6-12 months, it may be operated.
 - ➤ incidentally encountered GISTs < 2 cm → watchful waiting and surveillance for such very small GISTs might be reasonable.</p>
 - ➢ for patients with KIT-positive unresectable and/or metastatic GIST → Medical Management:
 - first line → Imatinib mesylate is an oral adenosine triphosphate (ATP) competitive TKI that selectively inhibits the activity of KIT, PDGFRA.
 - It is effective in 80% of patients and on average will control the disease for about two years.
 - imatinib may be used as an adjuvant therapy after surgery to reduces the risk of the cancer returning
 - second-line → In case of imitanib resistance: patients can be switched directly from low-dose imatinib (400 mg/day) to another TKI, such as the only approved second-line therapy, sunitinib.
 - 3rd line → Regorafenib (if imatinib and sunitinib are not effective or not tolerated)

Menetrier's disease

- A rare condition associated with giant gastric folds, predominantly in the fundus and body of the stomach.
- Histologically there is hyperplasia of the gastric pits, gland atrophy and an increase in overall mucosal thickness.
- Hypochlorhydria is usually present.
- Patients often complain of epigastric pain
- protein loss from the gastric mucosa can result in mild hypoalbuminaemia.
- some patients improve spontaneously, whereas in others this can be a premalignant state.
- Antisecretory drugs such as proton-pump inhibitors can be tried for symptom relief.

Bowel conditions

Dyspepsia

Causes of dyspepsia

- Gastro-oesophageal reflux disease (GORD) (15 25%)
- Gastric and duodenal ulcers (15 25%) and
- Stomach cancer (2%).
- The remaining 60% are classified as non-ulcer dyspepsia (NUD).
- Drugs causing dyspepsia
 - > NSAIDs (ibuprofen is associated with the lowest risk of peptic ulcer disease)
 - bisphosphonates
 - > steroids

- 430
- The following drugs may cause reflux by reducing lower oesophageal sphincter (LOS) pressure
 - calcium channel blockers*
 - nitrates*
 - * *calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS.
 - theophyllines

Indications of **Urgent** referral for an endoscopy (i.e. within 2 weeks). (NICE 2015)

- dysphagia
- upper abdominal mass consistent with stomach cancer
- · Any sign of chronic gastrointestinal bleeding
- Persistent vomiting
- · Iron deficiency anaemia,
- Suspicious barium meal.
- Progressive unintentional weight loss
- Patients aged ≥ 55 years who've got weight loss, AND any of the following:
 - upper abdominal pain
 - > reflux
 - dyspepsia

Non-urgent

- Patients with haematemesis
- Patients aged >= 55 years who've got:
 - > treatment-resistant dyspepsia or
 - upper abdominal pain with low haemoglobin levels or
 - raised platelet count with any of the following: nausea, vomiting, weight loss, reflux, dyspepsia, upper abdominal pain
 - nausea or vomiting with any of the following: weight loss, reflux, dyspepsia, upper abdominal pain

Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

- This can be summarised at a step-wise approach
 - 1. Review medications for possible causes of dyspepsia
 - 2. Lifestyle advice
 - 3. Trial of full-dose proton pump inhibitor for one month OR a 'test and treat' approach for *H. pylori*
- lifestyle advice
 - ⇒ avoid known precipitants: eg: smoking, alcohol, coffee, chocolate, fatty foods and being overweight
 - ⇒ Raising the head of the bed and having a main meal well before going to bed may help some people.
- Testing for H. pylori infection
 - initial diagnosis: NICE recommend using a carbon-13 urea breath test or a stool antigen test, or laboratory-based serology 'where its performance has been locally validated'
 - test of cure: carbon-13 urea breath test
- cognitive behavioural therapy and psychotherapy, may reduce dyspeptic symptoms in the short term in individual people.
- If H pylori has been excluded and symptoms persist, offer either a low-dose PPI or an H₂RA for 4 weeks.

Malabsorption

Features

- Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss.
- The presence of anaemia with low albumin raises the possibility of malabsorption

Causes may be broadly divided into:

- 1. intestinal causes (e.g. villous atrophy),
 - coeliac disease
 - Crohn's disease
 - > tropical sprue
 - Whipple's disease
 - Giardiasis
 - > brush border enzyme deficiencies (e.g. lactase insufficiency)
- 2. pancreatic causes (deficiency of pancreatic enzyme production or secretion)
 - > chronic pancreatitis
 - cystic fibrosis
 - pancreatic cancer
- 3. **biliary causes** (deficiency of bile-salts needed for emulsification of fats)
 - biliary obstruction
 - primary biliary cirrhosis
- 4. Other causes
 - bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop)
 - lymphoma
 - short bowel syndrome
 - Does not develop unless more than two thirds of the small intestine have been removed.
 - features include:
 - Abdominal pain
 - Diarrhea and steatorrhea
 - Fluid depletion
 - Weight loss and malnutrition
 - Fatique
 - complications caused by malabsorption of vitamins and minerals
 - Hyperoxaluria occurs both in patients with an ileal resection and in patients with a short bowel who have had a distal small bowel resection (for example, Crohn's disease, infarcted bowel).
 - ⇒ What is the most effective advice in preventing further renal calculi? → Dietary exclusion of chocolate, tea, rhubarb and spinach

D-xylose test

- D-xylose is a monosaccharide which is absorbed through the small intestines and excreted through the kidneys.
- D-xylose test is helpful in differentiating between structural and functional causes of malabsorption.
 - structural (e.g. Celiac disease, Crohn disease) or functional (e.g. pancreatic insufficiency)
- An abnormally low excretion of D-xylose is indicative of a structural pathology.
- This test distinguishes between malabsorption due to small-intestinal diseases and malabsorption due to pancreatic exocrine insufficiency.
- A 5-hour urinary excretion of 5 g or greater is normal following the oral administration of 25 g of D-xylose to a well-hydrated subject.
- Decreased xylose absorption and excretion are found:
 - In patients with damage to the proximal small intestine

- When there is bacterial overgrowth in the small intestine (the bacteria catabolise the xylose)
- Patients with pancreatic steatorrhoea (chronic pancreatitis) usually have normal xylose absorption.
- Abnormal results might be encountered in renal failure, in the elderly and in patients with ascites due to an excretion defect rather than malabsorption.

Diarrhoea (NICE 2012)

- Diarrhoea is defined as the abnormal passage of loose or liquid stools more than 3 times daily or a volume of stool greater than 200 g/day.
- Diarrhoea is considered to be chronic if it persists for more than 4 weeks.

Jejunal villous atrophy

Causes of villous atrophy (other than coeliacs): tropical sprue, Whipple's, lymphoma, hypogammaglobulinaemia

Causes

- coeliac disease
- tropical sprue
- hypogammaglobulinaemia
- gastrointestinal lymphoma
- Whipple's disease
- cow's milk intolerance

Coeliac disease

Coeliac disease - tissue transglutaminase antibodies first-line test

- Caused by sensitivity to the protein gluten.
- due to T cell mediated hypersensitivity reaction
- Mechanism: repeated protein gluten exposure \rightarrow villous atrophy \rightarrow malabsorption.
- Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis).
- It is strongly associated with HLA-DQ2 (95% of patients) and HLA-B8 (80%) as well as HLA-DR3 and HLA-DR7
- The prevalence of coeliac disease in Europe between 1:100 and 1:300.
- It presents at any age but in adults the commonest age of presentation is 20s and 30s.
- Women are slightly more commonly affected.
- The action of tissue transglutaminase on alpha-gliadin generates epitopes to CD4+ Tlymphocytes, which provoke an inflammatory response in the intestinal wall.

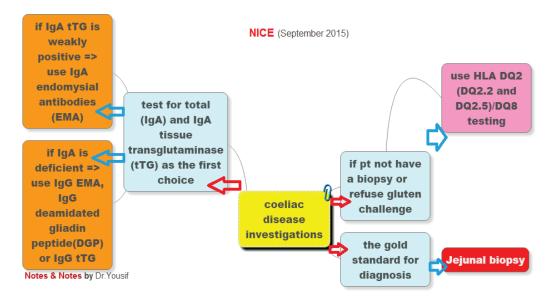
In 2009 NICE suggest that the following patients should be screened for coeliac disease:

Signs and symptoms	Conditions
 Chronic or intermittent diarrhoea Failure to thrive or faltering growth (in children) Persistent or unexplained gastrointestinal symptoms including nausea and vomiting Prolonged fatigue ('tired all the time') Recurrent abdominal pain, cramping or distension Sudden or unexpected weight loss Unexplained iron-deficiency anaemia, or other unspecified anaemia 	 Autoimmune thyroid disease Dermatitis herpetiformis Irritable bowel syndrome Type 1 diabetes First-degree relatives (parents, siblings or children) with coeliac disease

Associated conditions:

- Insulin-dependent diabetes mellitus,
- hypothyroidism,
- · chronic liver disease and
- · fibrosing alveolitis

Investigations



Diagnosis

- Diagnosis is made by a combination of immunology and jejunal biopsy. Villous atrophy and immunology normally reverses on a gluten-free diet.
- If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least 6 weeks prior to testing.

Immunology

- tissue transglutaminase (TTG) antibodies (IgA) are the first-choice
 - > Selective IgA deficiency is more common in patients with coeliac disease.

- > For this reason, IqA levels should be checked when serological tests are ordered.
- ➤ If the patient has selective IgA deficiency → tissue transglutaminase IgG can be measured.
- Patients normally need to be following a gluten-free diet for at least 6 months before the serology becomes negatives.
- endomyseal antibody (IgA) → 90% sensitive and almost 100% specific.
 - Anti-endomysial antibodies are sensitive and specific, but miss the disease in about 5% of the population who are IgA deficient.
- anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE
- · anti-casein antibodies are also found in some patients

Jejunal biopsy

- duodenal biopsies are the gold standard for diagnosis:
 - villous atrophy
 - crypt hyperplasia
 - > increase in intraepithelial lymphocytes
 - > lamina propria infiltration with lymphocytes
 - > Appearances may resemble severe tropical sprue

Rectal gluten challenge has been described but is not widely used

Subtotal villous atrophy is seen in a number of conditions other than coeliac disease such as:

- Severe tropical sprue
- Cow's milk/sova sensitivity in children
- Gastroenteritis
- Whipple's disease
- Hypogammaglobulinaemia
- Neomycin therapy
- Laxative abuse
- Norwalk agent.

Other investigations

- Imaging
 - > Which would most likely seen on abdominal radiograph with barium contrast?
 - Decreased jejunal folds, increased ileal folds
 - imaging and biopsy of the GI mucosa show a characteristic blunting of jejunal villi. This is often associated with a compensatory" jejunization" of the ileum to enhance nutrient absorption.
- Screen for other related autoimmunities
 - In a patient with newly diagnosed celiac disease, it is important to screen for other related autoimmunities as well, e.g. type 1 diabetes mellitus and autoimmune thyroiditis.

Management

- gluten-free diet.
 - > Gluten containing cereals include:
 - wheat: bread, pasta, pastry
 - barley: beer
 - whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease
 - rye
 - oats (some patients with coeliac disease appear able to tolerate oats)
 - > Some notable foods which are gluten-free include:
 - Rice
 - Potatoes
 - corn (maize)

follow-up

Tissue transglutaminase antibodies may be checked to check compliance with a gluten free diet

Associations and Complications

If the patient still symptomatic despite being compliant with a gluten free diet → think of T Cell lymphoma

- Enteropathy associated **T Cell lymphoma** (EATL)
 - ⇒ is a form of Non-Hodgkin's lymphoma
 - coeliac disease increase the risk of developing EATL within the 1st year of diagnosis, however with a strict gluten free diet, the risk returns to that of the general population after this point.
- · Recurrent mouth ulcers
- Hyposplenism (Splenic atrophy): seen in 50% of cases and responds poorly to gluten withdrawal.
- selective Ig A deficiency
- Small-bowel ulceration is associated with ulcerating jejunitis, but not colonic or gastric
 ulcers.

MRCPUK-part-1-January 2016 exam: Why do patients with coeliac disease require regular immunisations?

→ Functional hyposplenism

Whipple's disease

Whipple's disease: jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

- Whipple's disease is a rare multi-system disorder
- Caused by Tropheryma whippelii, a Gram positive bacterium

Epidemiology

- more common in those who are HLA-B27 positive
- most common in white males aged 40-50 years
- rarely is described in women (M:F ratio 9:1).

Pathophysiology

 Malabsorption in Whipple disease is caused by <u>macrophages</u> in the small bowel lamina propria compressing the lacteals.

Features

- · malabsorption: diarrhoea, weight loss
- · large-joint arthralgia
- lymphadenopathy
- skin: hyperpigmentation and photosensitivity
- · pleurisy, pericarditis
- neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus, characteristic oculo-masticatory movements

Investigation

- jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules
- •
- presence of *T. whippelei* DNA in tissue by PCR.

Management

- oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin
- · other option:
 - initial two week course of parenteral penicillin and streptomycin; followed by a prolonged course (one year) of tetracycline.

Tropical Sprue

- most common in the Carribbean and the Far-East.
 - ⇒ occurs in tropical regions, predominantly central America and South-Eastern Asia.
- characterized by a picture of small intestinal malabsorption and the cause is thought to be infectious in origin.
 - ⇒ It is thought that an initial GI infection results in small bowel stasis, opportunistic colonisation by organisms such as coliforms, and then a degree of villous atrophy leading to malabsorption and B12, folate deficiency.
 - deficiency in folate contributes to greater mucosal injury.

Features

- Patients classically have a history of recent travel to a tropical area
- present with indigestion, cramps within 2 or 3 weeks after an acute enteric infection.
- Megaloblastic anemia due to folate or B12 deficiency is a common finding.

Diagnosis:

- Jejunal biopsy reveals:
 - Mild villous atrophy
 - ↑↑ villous crypts
 - Mononuclear cellular infiltrates
 - > Enlarged epithelial cells
 - Large nuclei caused by folate and/or vitamin B12 deficiency.
- barium swallow may show thickening of mucosal folds

Treatment:

- The main treatment for tropical sprue is broad-spectrum antibiotics (i.e., tetracycline) and vitamin supplementation (i.e., folic acid, vitamin B12).
 - > Tetracyclines 250mg qds up to 6 months
 - Ampicillin may be used as an alternative in patients who are intolerant of tetracyclines.
 - > Folate and B12 deficiencies should also be corrected
- Complete recovery is possible with appropriate therapy.

<u> Irritable bowel syndrome (IBS)</u>

Insoluble sources of fibre such as bran and wholemeal should be avoided in IBS

Pathophysiology

- Studies looking at dietary restriction followed by reintroduction suggest <u>food intolerance</u> in 30-60% of patients with IBS.
- increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation.
- <u>Proliferation of intestinal mast cells</u> is a proposed mechanism by which food and stress may trigger symptoms.

Feature

- features supporting a diagnosis of IBS include:
 - ➤ A long history with a relapsing and remitting course
 - Exacerbations triggered by life events
 - Symptoms aggravated by eating, and
 - Coexistence of anxiety and depression.
- features which suggest organic disease rather than IBS include:
 - > Fever
 - Onset of symptoms in old age
 - Progressive deterioration
 - Weight loss
 - Rectal bleeding (not due to fissures or haemorrhoids)
 - Steatorrhoea, and
 - Dehydration.

Diagnosis (NICE 2008)

- The diagnosis of IBS should be considered if the patient has had the following for at least 6 months:
 - 1. abdominal pain, and/or
 - 2. bloating, and/or
 - 3. change in bowel habit
- A positive diagnosis of IBS should be made if the patient has abdominal pain relieved by defecation or associated with altered bowel frequency stool form, in addition to 2 of the following 4 symptoms:
 - 1. altered stool passage (straining, urgency, incomplete evacuation)
 - abdominal bloating (more common in women than men), distension, tension or hardness
 - 3. symptoms made worse by eating
 - 4. passage of mucus
- Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis
- Red flag features should be enquired about:
 - 1. rectal bleeding
 - 2. unexplained/unintentional weight loss
 - 3. family history of bowel or ovarian cancer
 - 4. onset after 60 years of age
- Also on clinical examination the other 'red flag' indicators are:
 - Anaemia
 - Abdominal mass
 - Rectal mass, and
 - > Inflammatory markers for inflammatory bowel disease.
- Suggested primary care investigations are:
 - full blood count
 - ➤ ESR/CRP
 - coeliac disease screen (tissue transglutaminase antibodies)

Management (NICE 2015).

NICE recommend avoiding lactulose in the management of IBS

First-line pharmacological treatment - according to predominant symptom

- pain: antispasmodic agents
 - > Pinaverium is used to reduce the pain duration associated with (IBS).

- diarrhoea: loperamide is first-line
- · constipation: laxatives but avoid lactulose
- For patients with constipation who are not responding to conventional laxatives linaclotide
 may be considered, if:
 - > optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
 - > they have had constipation for at least 12 months

Second-line pharmacological treatment

 low-dose tricyclic antidepressants (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors

Other management options

- psychological interventions if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy
- complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

General dietary advice

- · have regular meals and take time to eat
- · avoid missing meals or leaving long gaps between eating
- drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas
- · restrict tea and coffee to 3 cups per day
- · reduce intake of alcohol and fizzy drinks
- consider limiting intake of high-fibre food (for example, whole meal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice)
- reduce intake of 'resistant starch' often found in processed foods
- limit fresh fruit to 3 portions per day
- for diarrhoea, avoid sorbitol
- for wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

Fibre

- There are two main types of fibre soluble fibre (which dissolves in water) and insoluble fibre
- It is soluble fibre rather than insoluble fibre that seems to help ease symptoms in some cases.
 - A diet high in soluble fibre is often prescribed for the treatment of IBS
 - Dietary sources of soluble fibre include oats, ispaghula (psyllium), nuts and seeds, some fruit and vegetables and pectins.
 - A fibre supplement called ispaghula powder is also available from pharmacies and health food shops. This seems to be the most beneficial type of supplement.
- Insoluble fibre is chiefly found in corn (maize) bran, wheat bran and some fruit and vegetables. In particular, avoid bran as a fibre supplement.

Malnutrition

- Pathophysiology
 - **Food intolerance (in 30-60% of patients with (IBS).)**
 - increased intestinal contractile and electrical activity with increased sensitivity to visceral stimulation.
 - Proliferation of intestinal mast cells is a proposed mechanism by which food and stress may trigger symptoms.
- definition: NICE define malnutrition as the following:
 - 1. a Body Mass Index (BMI) of less than 18.5; or

- 2. unintentional weight loss greater than 10% within the last 3-6 months; or
- a BMI of less than 20 and unintentional weight loss greater than 5% within the last 3-6 months
- Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes.
- Screening for malnutrition if mostly done using MUST (Malnutrition Universal Screen Tool).
 - > it should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores (The Waterlow score is used to estimate the risk of a patient developing a pressure sore)
 - > it takes into account BMI, recent weight change and the presence of acute disease
 - categorises patients into low, medium and high risk
- Management of malnutrition is difficult. NICE recommend the following points:
 - dietician support if the patient is high-risk
 - a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure
 - > if ONS are used they should be taken between meals, rather than instead of meals

Waterlow score is used to estimate the **risk of a patient developing a pressure sore**, this includes an assessment of malnutrition as one of it's components

Lactose intolerance

- Lactase acts on lactose to generate glucose and galactose.
- more common in Asian, and East Asian races.
 - South-east Asian people, like the Vietnamese, Thais, and Chinese, have a very high prevalence of lactase deficiency.
- Any GI infection may precipitate the diagnosis of lactose intolerance, as gut flora may be altered by large bowel bacterial or viral load, as well as the treatment of infection.
- A change from an Eastern to a Western high lactose diet may also reveal lactose intolerance.
- Many patients labelled as having IBS may suffer from undiagnosed lactose intolerance
- many medications use lactose as a binding and stabilising agent.
- Diagnosed with a DNA assay of the lactase gene along with a hydrogen breath test.
- Treatment of lactose intolerance is with careful replacement of lactase.

Functional constipation

- The Rome III criteria for functional constipation is as follows (it must include two or more of the following):
 - straining during at least 25% of defecations
 - > lumpy or hard stools in at least 25% of defecations
 - > sensation of incomplete evacuation for at least 25% of defecations
 - > sensation of anorectal obstruction/blockage for at least 25% of defecations
 - manual manoeuvres to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
 - support of the pelvic floor)fewer than three defecations per week
 - loose stools are rarely present without the use of laxatives, and
 - > insufficient criteria for irritable bowel syndrome.
- These criteria must be fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

Energy from food

- The amount of energy that may be derived from 1 gram of food is as follows:
 - > carbohydrates: 4 kcal
 - > protein: 4 kcal
 - fat: 9 kcal
- The amount of energy a food product contains is expressed in calories (kcal). In simple terms, per unit weight, fats contain twice as many calories as protein or carbohydrates.

Protein losing enteropathy

Definition

- excessive leakage of plasma proteins into the lumen of the GIT
- refers to any condition of the GIT that results in a net loss of protein from the body.

Causes

- lymphatic obstruction, (lymphatic leakage secondary to obstruction.): e.g.:
 - primary intestinal lymphangiectasia,
 - conditions associated with venous stasis such as right-sided heart failure.
- mucosal disease:
 - inflammatory exudation through mucosal damage:
 - inflammatory bowel diseases,
 - NSAID enteropathy.
 - GI malignancy.
 - increased permeability from non-erosive mucosal disease
 - amyloidosis,
 - GI infections.
 - rheumatic diseases,

Features

- The most common presenting symptom is swelling of the legs due to decreased plasma oncotic pressure.
 - > bilateral oedema from hypoproteinaemia is generalised and may be seen in the periorbital region as well as in the extremities
- diarrhoea

Investigations

- Measurement of α1-Antitrypsin in a sample of faeces
 - the most appropriate to confirm the diagnosis
 - Albumin is degraded by proteases in the gut; however, α1-antitrypsin is a plasma protein that is resistant to degradation by proteases (it is a protease inhibitor) and its measurement can indicate leakage of plasma proteins into the gut.
- Serum albumin
 - > albumin level <20 g/L (<2 g/dL) is usually required to cause peripheral oedema
 - > Finding of low serum albumin prompts investigation to determine whether the aetiology is due to loss in the urine, hepatic synthetic dysfunction, or gastrointestinal losses. History of significant diarrhoea in conjunction with ruling out alternative causes makes the diagnosis.

Treatment

Treat the underlying disease.

Enteral feeding

Definition

• Enteral feeding = any route of feeding that utilizes the patient's GI tract to deliver appropriate nutrition (differs from parenteral nutrition, which delivers nutrition intravenously, completely bypassing the GI tract)

Enteral nutrition VS parenteral nutrition

 Enteral nutrition is preferred to parenteral nutrition whenever feasible - if the GI tract is functional, use it - benefits include improved absorption, immunological benefits, and helps maintain a healthy and functional GI tract

Routes of enteral feeding:

- Short-term: nasogastric tubes
 - Consider gastric feeding unless upper GI dysfunction (then for duodenal or jejunal tube)
- Long-term (> 2–3 weeks): gastrostomy or jejunostomy tubes
 - Gastric feeding > 4 weeks consider long-term gastrostomy
 - gastrostomy tube:
 - mainly used in cases of proximal gastrointestinal tract obstruction to facilitate feeding.
 - If it withdrew accidentally, reinsertion of the tube as soon as possible would be the preferred action. However, it needs a good level of expertise to do this.
 - Therefore, in this case, insertion of a Foley's catheter is the best practice as it is easy to do, and this should preserve the opening of the skin and anterior abdominal wall muscles until a someone experience enough is available to re-insert the gastrostomy tube.

How to check NG placement?

- Check NG placement using aspiration and pH (check post pyloric tubes with AXR)
 - ➤ The first line investigation to confirm correct placement of a nasogastric tube is → pH testing of gastric aspirate using indicator paper
 - If the pH is between 1 and 5.5 then this is confirmatory evidence of correct placement.
 - If the pH reading is between 5.5 and 6 it is recommended that a second independent reading is made to confirm.
 - if aspirate pH ≥6 → nasogastric feeding tubes feeding cannot be commenced
 - If there is any doubt, then an appropriately interpreted chest x ray is a second line investigation.

Key points

- Identify patients as malnourished or at risk (see below)
- Identify unsafe or inadequate oral intake with functional GI tract
- Consider bolus or continuous feeding into the stomach
- PEG can be used 4 hours after insertion but should not be removed until >2 weeks after insertion.

Indications

- pre-operative
 - Surgical patients due to have major abdominal surgery: if malnourished, unsafe swallow/inadequate oral intake and functional GI tract then consider pre-operative enteral feeding.
- ITU patients
 - > ITU patients should have continuous feeding for 16-24h (24h if on insulin)
 - Consider motility agent in ITU or acute patients for delayed gastric emptying. If this doesn't work, then try post pyloric feeding or parenteral feeding.

Contraindications

- Mechanical ileus, bowel obstruction
- Acute abdomen (e.g., severe pancreatitis, peritonitis)
- Upper GI bleeding
- Mucositis
- Severe substrate malabsorption
- Congenital GI anomalies
- High-output fistulas
- Nonfunctional GI tract (e.g., gastroschisis, short bowel syndromes)

Patients identified as being malnourished

- BMI < 18.5 kg/m^2
- unintentional weight loss of > 10% over 3-6/12
- BMI < 20 kg/m² and unintentional weight loss of > 5% over 3-6/12

AT RISK of malnutrition

- Eaten nothing or little > 5 days, who are likely to eat little for a further 5 days
- Poor absorptive capacity
- · High nutrient losses
- · High metabolism

Causes of diarrhoea in patients receiving enteral nutrition:

- hyperosmolar feed
- · bacterial contamination
- · low feed temperature
- · reduced intestinal absorptive capacity
- · too rapid or irregular administration
- · lactose intolerance.

Causes of constipation in patients receiving enteral nutrition:

· Inadequate fluid replacement

Refeeding syndrome

Refeeding syndrome

hypophosphataemia

Give 50% of normal energy intake in starved patients (> 5 days) to avoid refeeding syndrome

Definition:

 Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation (≥ 5 days).

Pathophysiology:

- When malnourished, the body uses endogenous fuel stores for energy and maintains serum electrolytes by redistribution from intracellular spaces.
- Exogenously administered glucose results in insulin release. This results in rapid uptake of glucose, potassium, phosphate and magnesium into cells, with dramatic falls in the extracellular concentrations.

Features

- Hypophosphataemia (symptoms are due predominantly to hypophosphataemia,)
- hypokalaemia
- hypomagnesaemia
- abnormal fluid balance
- Due to understood reasons, the body retain fluid → ↑ extracellular space → ↑cardiac work
 → acute heart failure.

- · neurological problems resulting in:
 - Oedema

Coma

Lethargy

Convulsions, and

Confusion

- Death.
- Nausea and diarrhoea is also common due to gut intolerance.

Prevention (NICE 2006)

- Identify patients at a high-risk of developing refeeding syndrome
 - > Patients are considered high-risk:
 - if one or more of the following:
 - 1. BMI < 16 kg/m^2
 - 2. unintentional weight loss >15% over 3-6 months
 - 3. little nutritional intake > 10 days
 - 4. hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding (unless high)
 - If two or more of the following:
 - 1. BMI < 18.5 kg/m^2
 - 2. unintentional weight loss > 10% over 3-6 months
 - 3. little nutritional intake > 5 days
 - 4. history of: alcohol abuse, drug therapy including insulin, chemotherapy, diuretics and antacids
- Decrease oral calorific intake to less than 50% of the recommended amount.
 - NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than 50% of requirements for the first 2 days.
 - limit initial dietary intake to 1000–1500 kcal/day

Management

- Correcting electrolyte abnormalities aggressively
 - it may be preferable to provide electrolyte replenishment prior to commencing calorific intake

A patient with a history of **alcoholism** is admitted for **re-feeding**. Which component of the feed may need to be reduced **to avoid encephalopathy**?

- → Protein
 - protein content of feeds should be strictly managed in patients with alcoholism.
 - Protein rich feeds → ↑ total ammonia burden→ ↑ risk of encephalopathy.

Melanosis coli

Diarrhoea - biospy shows pigment laden macrophages = laxative abuse

- Melanosis coli is a disorder of pigmentation of the bowel wall.
- Causes
 - It is associated with laxative abuse, especially anthraquinone compounds such as senna
 - This phenomenon is seen in over 70% of persons who use anthraquinone laxatives (for example, cascara sagrada, senna, and frangula) within several months of use.
 - Also alternative "medicine" drugs contain ingredients like cascara which contain anthraquinones.
 - The modern laxatives such as liquid paraffin and polyethylene glycol do not cause these changes.
- Pathophysiology

- Chronic use of anthraquinone laxatives cause injury to the colonic epithelium, with generation of **lipofuscin pigment**. This pigment is subsequently engulfed by the macrophages to give rise to the histological picture.
- Diagnosis
 - Melanosis coli is a histological diagnosis made from rectal biopsy material which shows numerous macrophages filled with brown pigment within the lamina propria.
 - Histology demonstrates pigment-laden macrophages
 - The macroscopic appearance varies from deep black pigmentation to reticulated brown discolouration.
- Treatment
 - The condition is benign and reversible on stopping the laxatives.

Mesenteric ischaemia (ischaemic colitis)

The two most common symptoms of ischemic colitis are severe abdominal pain and hematochezia (passage of fresh blood through the anus).

- Mesenteric ischaemia is primarily caused by arterial embolism resulting in infarction of the colon
- More likely occur in areas such as the splenic flexure that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.
 - > especially the **superior mesenteric artery**.

Predisposing factors

- increasing age
- atrial fibrillation
- · other causes of emboli: endocarditis
- · cardiovascular disease risk factors: smoking, hypertension, diabetes

Features

- abdominal pain
 - abdominal pain exacerbated by eating is suggestive of mesenteric ischaemia.
 - Pain that is disproportionately severe compared to the abdominal findings is characteristic.
- · rectal bleeding
- diarrhoea
- fever
- bloods typically show an elevated WBC associated with acidosis
- Acute mesenteric ischaemia is a cause of elevated amylase that is unrelated to pancreatitis.
- Elevated serum lactate also suggests ischaemic aetiology.

Diagnosis

- CT scanning: the imaging modality of choice, with a sensitivity and specificity over 90%.
 - If the presentation is clearly of acute bowel ischaemia then a CT angiography would be the best test.
 - the presentation is consistent with several other possible causes of bloody diarrhoea and abdominal pain (i.e. acute colitis), Flexible sigmoidoscopy would be the best investigation safer than colonoscopy (relative contraindication in active colitis), allowing biopsies to be taken and the viewing of a possible pseudomembrane.
 - Occasionally the mucosa has a characteristic appearance.
 - Biopsies show ulceration and a polymorphonuclear infiltrate.
 - Haemosiderin-laden macrophages are characteristic but uncommon.
- Angiography: if the diagnosis is in doubt.

- Mucosal edema can be seen as the <u>thumbprinting</u> sign on plain abdominal radiograph and barium enema.
- Flexible sigmoidoscopy
 - > The finding of <u>ulceration which spares the rectum is typical</u>
 - > ulceration extending to the splenic flexure corresponds with the arterial supply of the inferior mesenteric artery.

Management

- supportive care
- balloon angioplasty and stenting
 - the preferred treatment for hemodynamically stable patients with acute mesenteric ischemia who do not present with signs or symptoms of advanced intestinal ischemia (peritonitis, sepsis) because this procedure is minimally invasive and studies suggest similar efficacy to open surgical treatment.
- laparotomy and bowel resection
 - laparotomy is reserved for acutely ill patients who are hemodynamically unstable or have evidence of peritonitis (rebound tenderness and involuntary guarding).

MRCPUK-part-1-jan-2018: Which part of the bowel is most prone to ischaemic colitis?

- → Splenic flexure
 - because it receives its blood supply from terminal branches of the superior mesenteric and inferior mesenteric arteries, creating a watershed area.

Small bowel bacterial overgrowth syndrome (SBBOS)

Definition

 (SBBOS) is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms of bloating, abdominal distension and diarrhoea

.Risk factors for SBBOS

- · neonates with congenital gastrointestinal abnormalities
- scleroderma
- absent gastric acid secretion
- small bowel diverticulae
- · fistulae between the small and large bowel
- small bowel strictures
- diabetes mellitus (diabetic neuropathy)
- adhesions.

Features: It should be noted that many of the features overlap with irritable bowel syndrome:

- chronic diarrhoea
- bloating, flatulence
- abdominal pain
- Biochemically there is classically a low vitamin B₁₂ level and normal or elevated folate level as a result of bacterial metabolism of B₁₂ to folate.

Steatorrhoea and flatulence are classic presenting features of small bowel bacterial overgrowth.

Investigation

- The gold standard investigation of bacterial overgrowth is small bowel aspiration and culture
- Other possible investigations include:
 - hydrogen breath test

- > 14C-xylose breath test
- > 14C-glycocholate breath test: used increasingly less due to low specificity
- In practice many clinicians give an empirical course of antibiotics as a trial

Management

- correction of underlying disorder
- antibiotic therapy: rifaximin is now the treatment of choice due to relatively low resistance
- Co-amoxiclay or metronidazole are also effective in the majority of patients.

Spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis - intravenous cefotaxime

- (SBP) is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis. most commonly seen in alcoholic cirrhosis
- typically caused by aerobic gram negative bacteria. (usually Escherichia coli, Klebsiella)
 - sponteanous bacterial peritonitis is almost without exception caused by a single organism.

Diagnosis

- paracentesis: neutrophil count > 250 cells/ul
 - Sending some ascitic fluid in blood culture bottles increases the yield.
- high serum ascites albumin gradient (SAAG) (>11 g/L) ascitic fluid and the white cells will be predominantly neutrophils (>500 WBCs/mm³ and >50% neutrophils).

Management:

- > intravenous cefotaxime is usually given
- other option: IV piperacillin-tazobactam
 - It is important to start antibiotics promptly pending the results of an ascitic analysis.
- Antibiotic prophylaxis should be given if:
 - patients who have had an episode of SBP
 - patients with fluid protein <15 g/l and either Child-Pugh score of at least 9 or hepatorenal syndrome
 - Norfloxacin is recommended for short term prophylaxis.

Prognosis

- Alcoholic liver disease is a marker of poor prognosis in SBP.
- Has poor prognostic significance with a one-year survival after a diagnosis of between 30-50%.
 - An episode of spontaneous bacterial peritonitis carries a two-year mortality rate of 50%.

Differential diagnosis

- pancreatic ascites (eg. Acute pancreatitis)
 - elevated fluid amylase helps confirm this (particularly the characteristic way in which it is in excess of the serum value).
 - The low lactate dehydrogenase (<225 IU/L) helps exclude a polymicrobial ascitic fluid infection which has similar findings
 - no mention of finding any organisms on the Gram stain.
 - Bacterial growth occurs in about 80% of specimens with polymorphonuclear (PMN) count of >250 cells/mm3.
 - Ascitic fluid analysis demonstrates a low serum albumin ascites gradient (SAAG) (<11 g/L).

- Cirrhosis and spontaneous bacterial peritonitis are both characterised by a high SAAG (>11 g/L) and are differentiated from each other on the basis of white cell count, Gram stain and culture results.
- > secondary bacterial peritonitis (ruptured viscus or loculated abscess).
 - Lactate dehydrogenase >225mU/L, glucose <50mg/dL, total protein >1g/dL and multiple organisms on gram stain suggest secondary bacterial peritonitis (ruptured viscus or loculated abscess).
- Chylous ascites
 - A high level of triglycerides confirms chylous ascites.
- elevated amylase level suggest pancreatitis or gut perforation.
- elevated bilirubin level suggest biliary or gut perforation.

Abdominal tuberculosis (Tubercular peritonitis)

Features

- · risk of tuberculosis
- should always be suspected in the severely malnourished patient
- Constitutional symptoms are common, including fever, anorexia and weight loss.
- extensive lymphadenopathy.

Investigations

- The cut-off for considering ascitic fluid to be exudative would be 30 g/l, but in the setting of hypoproteinaemia, this is less relevant.
- The marked increase in white cell count is strongly supportive of a diagnosis of infective ascites.

Diagnosis

- The most sensitive test to establish the diagnosis is visually directed (laparoscopic) peritoneal biopsy with histology and culture for TB.
- Although PCR of ascitic cells/fluid has increased non-invasive diagnosis, the best yield remains from laparoscopy and peritoneal biopsy, which in recent series led to a diagnosis in 95% of cases.
- An alternative in this setting might be to perform fine needle aspiration or excision biopsy of one of the palpable lymph nodes.
- The diagnostic yield of ascitic culture for mycobacteria is very low (<10%) even with closed culture systems.

Which investigation is most likely to yield a diagnosis?

→ Laparoscopy and peritoneal biopsy

VIPoma

VIPoma: WDHA syndrome Watery Diarrhea, Hypokalemia, Achlorhydria.

VIP (vasoactive intestinal peptide)

- · source: small intestine, pancreas
- · stimulation: neural
- actions:
 - > stimulates water and electrolytes secretion by pancreas and intestines,
 - inhibits gastric acid and pepsinogen secretion
 - > peripheral vasodilation,
 - > potentiates acetylcholine action on salivary glands.

VIPoma

- 90% arise from pancreas
- large volume diarrhoea, <u>secretory</u> diarrhoea ('pancreatic cholera')
 - ➤ The normal daily stool weight is 250–300 g
 - > A stool volume of <700 mL/d excludes the diagnosis of VIPoma.
 - What is the most likely mechanism of diarrhoea?
 - Secretory due to enterocyte stimulation
- weight loss
- dehydration
- hypokalaemia, hypochlorhydria. Achlorhydria
- hypokalaemic acidosis (loss of alkaline secretions)
- mildly raised glucose.
- raised plasma pancreatic polypeptide
- · abdominal colic
- cutaneous flushing
- · raised plasma VIP

Volvulus

- Volvulus defined as torsion of the colon around it's mesenteric axis resulting in compromised blood flow and closed loop obstruction.
- Sigmoid volvulus (around 80% of cases) describes large bowel obstruction caused by the sigmoid colon twisting on the sigmoid mesocolon. A similar problem may also occur at the caecum (20% of cases).
- In most people (around 80%) the caecum is a retroperitoneal structure so not at risk of twisting. In the remaining minority there is however developmental failure of peritoneal fixation of the proximal bowel putting these patients at risk of caecal volvulus.

Sigmoid volvulus associations	Caecal volvulus associations
 older patients chronic constipation Chagas disease neurological conditions e.g. Parkinson's disease, Duchenne muscular dystrophy psychiatric conditions e.g. schizophrenia 	□ all ages □ adhesions □ pregnancy

Features

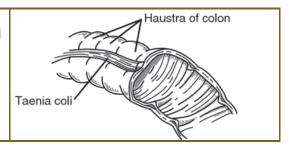
- constipation
- abdominal bloating
- abdominal pain
- nausea/vomiting

Diagnosis

- usually diagnosed on the abdominal film
 - The most helpful early diagnostic tool of intestinal obstruction is the plain abdominal X-ray.
- · sigmoid volvulus:
 - large bowel obstruction (large, dilated loop of colon, often with air-fluid levels) + coffee bean sign (omega sign)
- caecal volvulus:
 - small bowel obstruction may be seen

Sigmoid volvulus

The most important feature of a sigmoid volvulus rather than a large redundant distended loop of sigmoid colon is the absence of haustra.



Coffee Bean Sign Sigmoid volvulus

Massively dilated sigmoid loop





Management

- sigmoid volvulus:
 - > rigid sigmoidoscopy with rectal tube insertion
- caecal volvulus:
 - > management is usually operative. Right hemicolectomy is often needed

Imaging in bowel obstruction

Looking for small and large bowel obstruction is one of the key indications for performing an abdominal film.

Small bowel	Large bowel
Maximum normal diameter = 35 mm	Maximum normal diameter = 55 mm
Valvulae conniventes extend all the way across	Haustra extend about a third of the way across



Small bowel obstruction



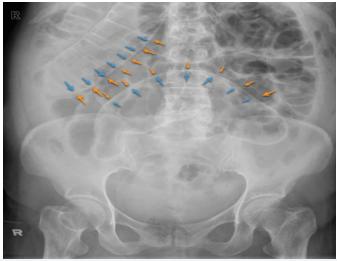
CT from a patient with small bowel obstruction secondary to adhesions. Distension of small bowel loops proximally (duodenum and jejunum) with abrupt transition to intestinal segment of normal caliber. Presence of small amount of free fluid intracavity.

Radiology: pneumoperitoneum

- An erect chest x-ray is a useful investigation in patients with an acute abdomen as it may demonstrate free air in the abdomen (pneumoperitoneum) - an abnormal finding suggestive of a perforated abdominal viscus (e.g. a perforated duodenal ulcer).
- Rigler's sign (double wall sign) may be seen on an abdominal film.
 CT is now the preferred method for detecting free air in the abdomen.



Erect chest x-ray with air visible under the diaphragm on both sides.



Abdominal x-ray demonstrates numerous loops of small bowel outlined by gas both within the lumen and free within the peritoneal cavity. Ascites is also seen, with mottled gas densities over bilateral paracolic gutters. In a normal x-ray only the luminal surface (blue arrows) should be visible outlined by gas. The serosal surface (orange) should not be visible as it is normally in contact with other intra-abdominal content of similar density (other loops of bowel, omentum, fluid). In this case gas abuts the serosal surface rendering it visible. As this film has been obtained

Dumping syndrome

- occur in up to 50% of patients who have undergone gastric bypass when high levels of simple carbohydrates are ingested.
- · early dumping syndrome
 - rapid onset , usually within 15 minutes of eating
 - > results from rapid emptying of food into the small bowel.
 - Due to the hyperosmolality of the food there are rapid fluid shifts from the plasma into the bowel leading to hypotension and a sympathetic nervous system response.
 - The presenting symptoms are often colicky abdominal pain, diarrhoea, nausea, and tachycardia.
 - > Treatment:
 - usually self-limiting and resolves within 7 to 12 weeks.
 - Patients should avoid foods high in simple sugar and replace them with high fibre, complex carbohydrates and protein-rich foods.
 - Small, frequent meals
 - leaving a 30 minute gap between solids and liquids
- Late dumping syndrome
 - occurs as a result of the hyperglycaemia and subsequent insulin response leading to hypoglycaemia which takes place two to three hours after a meal.
 - Symptoms include dizziness, fatigue, sweating, and weakness.
 - Management is similar to early dumping syndrome.

Small bowel lymphoma

Pain is the most common presenting feature of small bowel lymphoma

- Lymphoma comprises 15-20% of all small bowel tumours with the ileum most commonly affected.
- Primary lymphomas of the small bowel include
 - > mucosa-associated lymphoid tissue (MALT) lymphoma
 - diffuse large B cell lymphoma
 - immunoproliferative small intestinal disease (IPSID), and
 - enteropathy-associated T cell lymphoma (EATL).
- Patients with coeliac disease are at higher risk of T cell lymphoma.
- There is a male predominance
- the median age at presentation of 25 years.
- Patients may present with:
 - anorexia
 - weight loss
 - nausea and vomiting
 - > chronic pain
 - abdominal fullness
 - early satiety, and
 - constipation.
 - Findings on CT vary and may include multiple tumours, narrowing of the bowel lumen and mesenteric nodal masses.

Pancreatic conditions

Acute pancreatitis

Hypertriglyceridaemia (with level > 10 mmol/l) is a risk factor for acute pancreatitis

• acute inflammation of the pancreas → release of exocrine enzymes → auto-digestion. Pathophysiology

- Sequence of events leading to pancreatitis:
 - Intrapancreatic activation of pancreatic enzymes: secondary to pancreatic ductal outflow obstruction (e.g., gallstones, cystic fibrosis) or direct injury to pancreatic acinar cells (e.g., alcohol, drugs)
 - > Enzymatic autodigestion of pancreatic parenchyma
 - ➤ Attraction of inflammatory cells (neutrophils, macrophages) → release of inflammatory cytokines → pancreatic inflammation (pancreatitis)
- Sequelae of pancreatitis (depending on the severity of pancreatitis)
 - Capillary leakage: Release of inflammatory cytokines and vascular injury by pancreatic enzymes → vasodilation and increased vascular permeability → shift of fluid from the intravascular space into the interstitial space (third space loss) → hypotension, tachycardia→ distributive shock
 - ➤ Pancreatic necrosis: Uncorrected hypotension and third space loss → decreased organ perfusion → multiorgan dysfunction (mainly renal) and pancreatic necrosis
 - ➤ Hypocalcemia: Lipase breaks down peripancreatic and mesenteric fat → release of free fatty acids that bind calcium → hypocalcemia

Causes

The commonest causes in UK are gallstones and alcohol

The aetiology of acute pancreatitis should be determined in at least 80% of cases and no more than 20% should be classified as idiopathic

Popular mnemonic is **GET SMASHED**

- Gallstones
 - account for 50% of cases, with the majority of the rest being associated with alcohol.
 - For prediction of a biliary etiology, an ALT level has the highest positive predictive value of any biochemical test.
- Ethanol
 - Amylase/lipase levels are markedly elevated in gallstone pancreatitis (thousands), whereas less increased in alcoholic (hundreds)
 - raised mean corpuscular volume (MCV) suggests chronic high alcohol use
- **T**rauma
- Steroids
- Mumps (other viruses include Coxsackie B)
- Autoimmune (e.g. polyarteritis nodosa), Ascaris infection
- Scorpion venom
- Hypertriglyceridaemia, Hyperchylomicronaemia, Hypercalcaemia, Hypothermia
- ERCP (acute pancreatitis following ERCP should be treated with I.V fluids + analgesia)
- Drugs (azathioprine, mesalazine, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)
 - pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Hypertriglyceridaemia

- Definitions:
 - hypertriglyceridaemia > 1.7 mmol/L.
 - Severe hypertriglyceridaemia >11.2-22.4 mmoL/L
 - > very severe as > 22.4 mmol/L.
- The third commonest cause of acute pancreatitis after alcohol and gallstones.
- Considered a risk factor for pancreatitis when triglyceride levels are above 11.2 mmol/l
- In a patient with hypertriglyceridaemia and acute abdominal pain, an amylase should be checked to exclude acute pancreatitis.

Features

- Patients typically present with severe epigastric pain which radiates to the back, and vomiting.
- there is often a systemic inflammatory response (SIRS)
- Serum amylase is classically raised three or more times normal,
- hypocalcaemia is relatively common.
- Raised bilirubin and/or serum aminotransferase suggest underlying gallstones.
- Cirrhosis results in a small shrunken liver and raised ALT and ALP (and gamma-GT if the cause is alcohol).
- Rare features associated with pancreatitis include:
 - ischaemic (Purtscher) retinopathy may cause temporary or permanent blindness
- Skin changes (rare)
 - Cullen's sign: periumbilical ecchymosis and discoloration (bluish-red)
 - Grey Turner's sign: flank ecchymosis with discoloration
 - Fox's sign: ecchymosis over the inguinal ligament

Marker of severity

- CRP is now a widely used marker of severity in acute pancreatitis.
- Other methods which have to correlate with prognosis include the Ranson criteria and APACHE II score

Prognosis

- Criteria of poor prognosis
 - ➤ There are a number of scoring systems which can be used to guide prognosis, but they are <u>unreliable within the first 48 hours of the illness.</u>
 - > Ranson's scoring system reflect prognosis associated with acute pancreatitis.
- Ranson's criteria on admission that signify a worse prognosis include:
 - > Criteria present at 0 hours:
 - Age >55 years old 1 point
 - WBC >16 ×10⁹ 1 point
 - Glucose >11.1 mmol/L 1 point
 - LDH >350 U/L 1 point
 - AST >250 U/L 1 point
 - Criteria present at 48 hours:
 - Hematocrit fall of 10% or greater 1 point
 - Urea rise of 1.8 mmol/L or more despite fluids 1 point
 - Serum Calcium <2 mmol/L 1 point
 - pO2 <60 mmHg 1 point (PaO2 of < 8.0 kPa)
 - Base deficit >4 meg/L 1 point
 - Fluid sequestration >6000 mL 1 point
- The mortality associated with severe acute pancreatitis → 20%
 - often due to sepsis or multiorgan failure.
- Hematocrit (Hct)

- Should be conducted at presentation as well as 12 and 24 hours after admissions
- ➤ ↑ Hct (due to hemoconcentration) indicates third space fluid loss and inadequate fluid resuscitation
- ➤ ↓ Hct indicates the rarer acute hemorrhagic pancreatitis
- The following portend a **poor prognosis** in patients with acute pancreatitis:

wcc	>15
Urea	>16
Calcium	<2.0
Glucose	>10
CRP	>150

Complications

- · ARDS (adult respiratory distress syndrome),
- · acute kidney injury
- disseminated intravascular coagulation (DIC).
 - due to pancreatic enzymes entering the blood and acting on coagulation factors, thereby activating them.
- · Pancreatic pseudocyst

Investigations

- lab
 - > Tests to confirm clinical diagnosis
 - Amylase is markedly raised, often in excess of four times the normal value.
 - nonspecific
 - Lipase: if ≥ 3 x the upper reference range → highly indicative of acute pancreatitis
 - More specific and preferred for the diagnosis
 - The enzyme levels are not directly proportional to severity or prognosis
 - > Tests to assess severity
 - Hematocrit (Hct)
 - Should be conducted at presentation as well as 12 and 24 hours after admissions

 - ❖ ↓ Hct indicates the rarer acute hemorrhagic pancreatitis
 - WBC count
 - Blood urea nitrogen
 - ↑ CRP and procalcitonin levels
 - ↑ ALT
- Images
 - Ultrasound
 - the most useful initial test
 - Main purpose: detection of gallstones and/or dilatation of the biliary tract (indicating biliary origin)
 - Signs of pancreatitis
 - Indistinct pancreatic margins (edematous swelling)

- Peripancreatic build-up of fluid ; evidence of ascites in some cases
- Evidence of necrosis, abscesses, pancreatic pseudocysts
- > CT with contrast
 - not routinely indicated
 - only when the diagnosis is in doubt
 - would be preferable to ultrasound in establishing the presence of inflammation (acute or chronic) of the pancreas and severity of disease
- Abdominal x ray
 - has NO role in acute pancreatitis
 - Sentinel loop sign:
 - dilatation of a loop of small intestine in the upper abdomen (duodenum/jejunum)
 - Colon cut off sign:
 - gaseous distention of the ascending and transverse colon that abruptly terminates at the splenic flexure
 - Evidence of possible complications:
 - pleural effusions,
 - pancreatic calcium stones;
 - helps rule out intestinal perforation with free air
 - may demonstrate calcification in **chronic** pancreatitis.

Follow-up:

All patients with persistent symptoms and greater than 30% pancreatic necrosis, and those
with smaller areas of necrosis and clinical suspicion of sepsis, should undergo image
guided <u>fine needle aspiration</u> to obtain material for culture <u>7-14 days after the onset of
pancreatitis</u>

Treatment

- supportive, and monitoring (often in the intensive care unit).
 - Fluid resuscitation: aggressive hydration with crystalloids (e.g., normal saline)
 - Analgesia: IV opioids (e.g., fentanyl)
 - > Bowel rest (NPO)and IV fluids are recommended until the pain subsides
 - Nasogastric tube insertion:
 - not routinely recommended:
 - indicated in patients with vomiting and/or significant abdominal distention
 - Nutrition
 - Begin enteral feeding (oral/nasogastric/naso-jejunal) as soon as the pain subsides
 - Total parenteral nutrition:
 - only in patients who cannot tolerate enteral feeds (e.g., those with persistent ileus and abdominal pain)
- if there is **gallstones**:
 - urgent ERCP when stable.
 - All should have a cholecystectomy either during the same admission or within four weeks depending on their clinical progress.

Systemic inflammatory response syndrome (SIRS)

Causes

- sepsis
- pancreatitis

Criteria

- SIRS is defined as **two or more** of the following:
 - 1. Temperature more than 38°C or less than 36°C
 - 2. Heart rate more than 90 beats/min
 - 3. Respiratory rate more than 20 breaths/min or PaCO2 less than 4.3 kPa
 - 4. WBC count 12,000/mm³, less than 4000/mm³, or more than 10% immature (bands) form.

Management

- resuscitation of the sick patient still follows the ABC algorithm:
 - 1. Airway
 - 2. Breathing
 - 3. Circulation.
 - Airway control and oxygen to maintain normal saturations is the first part of that algorithm.
 - Subsequent fluid resuscitation and treatment of the underlying cause can then be initiated.
 - The need for invasive monitoring and intensive care is then assessed, depending on the response to initial treatment.
- Early goal-directed therapy (EGDT) in cases of SIRS or septic shock is becoming increasingly recognised as potentially beneficial.
 - **EGDT** aims to:
 - increase organ perfusion through restoration of mean arterial pressure using inotropes if necessary,
 - maintaining central venous pressure (CVP),
 - maintaining oxygenation
 - using SjVO2 (jugular venous oxygen saturation) as a guide to oxygen utilisation at the tissue level.
 - ➤ If fluids are not achieving haemodynamic stability, and there is hypoperfusion (indicated by oliguria or lactataemia) → the most appropriate course of action → central line → vigorous resuscitation is indicated.
 - Insertion of a central line allows measurement of CVP, SjVO2 and the use of inotropes.
 - SjVO2 higher than 70% is indicative of organ hypoperfusion, as oxygen is not being extracted.
- Obtain blood cultures prior to antibiotic administration

Pancreatic pseudocysts

Definition

encapsulated collection of pancreatic fluid which develops 4 weeks after an acute attack
of pancreatitis; can occur in both acute and chronic pancreatitis

Pathophysiology

 pancreatic secretions leak from damaged ducts → inflammatory reaction of surrounding tissue → encapsulation of secretions by fibrous tissue

Clinical features

- Often asymptomatic
- Painless abdominal mass
- Pressure effects
- Gastric outlet obstruction (early satiety, non-bilious vomiting, abdominal pain)

• Bile duct obstruction with jaundice

Diagnostics

 abdominal ultrasound/CT/MRI → extrapancreatic fluid collection withinwell-defined wall/capsule, no solid cyst components detectable

Treatment

• Surgical/endoscopic; ultrasound/CT-guided percutaneous drainage

Chronic pancreatitis

Definition

 Chronic pancreatitis is an inflammatory condition, which can ultimately affect both the exocrine and endocrine functions of the pancreas.

Causes

- alcohol excess (80%)
 - what is the general mechanism by which alcohol induces the likely condition?
 - Alcohol increases acinar cell sensitivity to CCK (cholecystokinin), stimulating trypsinogen production in the cell
- Unexplained (20%)
- PRSS-1 mutation can cause a hereditary form of the disease.
 - It does this by allowing trypsin to be activated in the pancreas, thus causing enzymatic damage.
- SPINK-1 mutation can cause a hereditary form of the disease.
 - It does this by allowing trypsin to be activated in the pancreas, thus causing enzymatic damage.

Features

- pain is typically worse 15 to 30 minutes following a meal
- · steatorrhoea:
 - symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
 - ➤ Late manifestation (after 90% of the pancreatic parenchyma is destroyed)
- diabetes mellitus develops in the majority of patients. It typically occurs more than 20 years after symptom begin

Investigation

- abdominal x-ray shows pancreatic calcification in 30% of cases.
- CT is more sensitive at detecting pancreatic calcification.
 - > Sensitivity is 80%, specificity is 85%
 - More sensitive in moderate to advanced chronic pancreatitis
 - Malabsorption is only present in moderate to advanced chronic pancreatitis
 - abnormalities include:
 - pancreatic calcification,
 - pseudocyst formation and
 - ductal distortion.
 - > CT scanning is much less effective in the diagnosis of **early chronic pancreatitis** and a normal scan does not exclude the diagnosis.
- functional tests: faecal elastase may be used to assess exocrine function if imaging inconclusive
- Both 72-hour faecal fat estimation and D-xylose absorption testing are used for their ability to indicate the presence, or absence, of malabsorption, neither is diagnostic of an underlying condition.
 - associated with normal urinary D-xylose test findings

Management

- pancreatic enzyme supplements
 - Pancrelipase (Creon)
- Analgesia

- ➤ In a patient with chronic liver disease presented with features of decompensation associated with chronic pancreatitis → Naloxone
 - Patients with alcoholic liver disease are often surprisingly sensitive to opiate analgesia which should only be used with caution.
- antioxidants: limited evidence base one study suggests benefit in early disease

Complications

- Pancreatic pseudocysts
- · Splenic vein thrombosis
 - Occur in 10% of patients with chronic pancreatitis
 - ➤ Pathophysiology: inflammation of the splenic vein → thrombus formation → leftsided portal hypertension → gastric varices
 - > Clinical features: can present with upper GI bleeding, ascites, and splenomegaly
 - Diagnosis: ultrasound with doppler, CT/MR angiography
 - > Treatment
 - Acute: anticoagulation and/or thrombectomy
 - Chronic and symptomatic: splenectomy
- Pancreatic ascites
- Pancreatic diabetes
- Pancreatic cancer (especially in patients with hereditary pancreatitis)

Pancreatic cancer

- Pancreatic cancer is often diagnosed late as it tends to present in a non-specific way.
- Over 80% of pancreatic tumours are adenocarcinomas
- typically occur at the head of the pancreas.
 - most often found in the ductal cells in the head of the pancreas.

Associations

- · increasing age
- smoking
- diabetes
- chronic pancreatitis (alcohol does not appear an independent risk factor though)
- hereditary non-polyposis colorectal carcinoma
- multiple endocrine neoplasia
- BRCA2 gene
- · Jewish or African descent.

Features

- · classically painless jaundice
- however, patients typically present in a non-specific way with anorexia, weight loss, epigastric pain
- loss of exocrine function (e.g. steatorrhoea)
- atypical back pain is often seen
 - > the first symptom is often pain that radiates to the back.
 - because it is found very late when it has already impinged on other structures.
- migratory thrombophlebitis (Trousseau sign) is more common than with other cancers
 - > Migratory thrombophlebitis causes recurrent tender, palpable small blood clots that come and go in various locations on the body,

Investigation

- ultrasound has a sensitivity of around 60-90%
- high resolution CT scanning is the investigation of choice if the diagnosis is suspected
- Carbohydrate Antigen 19-9 (CA-19-9) is a tumour marker is usually used to monitor response to treatment and possible recurrance, rather than for diagnosis.

Management

• less than 20% are suitable for surgery at diagnosis

- a Whipple's resection (pancreaticoduodenectomy) is performed for resectable lesions in the head of pancreas.
 - > Side-effects of a Whipple's include dumping syndrome and peptic ulcer disease
- adjuvant chemotherapy is usually given following surgery
- ERCP with stenting is often used for palliation
 - relief of symptoms as soon as possible is the main objective of therapy.
 - Stenting relieves symptoms of itching and reverses jaundice in about 85% of patients.
 - Stents can be inserted during an ERCP or percutaneously in those with extensive disease or in those otherwise unsuitable for surgery.

Prognosis

• It has a very high mortality rate (approximately 1 year from diagnosis), usually because it is found very late when it has already impinged on other structures.

Biliary conditions

Ascending cholangitis

- Ascending cholangitis is a bacterial infection of the biliary tree.
- The most common predisposing factor is gallstones.

Features

- Charcot's triad (occurs in about 20-50% of patients)
 - 1. right upper quadrant (RUQ) pain, (70%)
 - 2. fever (the most common feature, seen in 90%)
 - 3. jaundice (60%)
- hypotension and confusion are also common
 - Combining these two additional symptoms to Charcot's triad results in Reynold's pentad.
- elevated alkaline phosphatase and elevated direct bilirubin suggest obstruction of the biliary tree

Investigation

- The initial imaging study is <u>ultrasonography</u>.
- The gold standard for diagnosis is (ERCP) endoscopic retrograde cholangiopancreatography.

Management

- · intravenous antibiotics
- endoscopic retrograde cholangiopancreatography (ERCP) after 24-48 hours to relieve any
 obstruction

Gallstones (Cholelithiasis)

Risk factors for biliary stones

- Cholesterol gallstones are thought to arise as a result of a triple defect:
 - 1. Super saturation of gallbladder bile (high in cholesterol, low in bile salts)
 - 2. Increased rate of cholesterol nucleation in the gallbladder
 - 3. Reduction in gallbladder contractility
- Predisposing factors to gallstone formation:
 - Older age
 - Female sex (oestrogens)
 - Oral contraceptive use
 - Cirrhosis (bile pigment stones)
 - ileal resection (by reducing entero-hepatic circulation and increasing bile salt loss)

- Clofibrate (by increasing biliary supersaturation)
- > rapid weight loss
- > Cholestyramine (by binding bile salts)
- Crohn's disease

Features

- most will be asymptomatic
- Classic symptoms include biliary colic, nausea, and/or vomiting
 - biliary colic: sharp, colicky pain made worse with fatty food due to ↑ release of CCK → contraction of gallbladder

Investigation

- liver function tests : obstructive jaundice
- Ultrasound
 - abdominal/right upper quadrant ultrasound is the test of choice for gallstone disease
 - ultrasound finding of a common bile duct dilatation is suggestive of an obstructing stone
 - Whilst ultrasound is a good preliminary investigation for common bile duct stones it lacks sensitivity.
 - > The sensitivity of ultrasound for detecting stones is significantly reduced during an episode of acute pancreatitis (around 70%) so repeating an ultrasound is a reasonable suggestion as it would perform better in the current clinical context than it had done previously. However, its ability to detect CBD stones remains poor.
 - MRI is highly effective in confirming the presence of common bile duct stones,
 - endoscopic ultrasound (EUS) is a suitable alternative.
 - CT does not perform well when compared to MRI.
- Radiographs
 - cannot rule out stone with negative radiograph because cholesterol stones are radiolucent
 - > pigment stones are radiopaque so may show up on radiograph
- Endoscopic retrograde cholangiopancreatography (ERCP), along with intra-operative cholangiography, is considered <u>the gold standard</u> for diagnosis of common bile duct stones.
 - However it is an invasive procedure associated with significant morbidity; thus it should ideally be performed as a therapeutic rather than diagnostic procedure.
 - The indication for ERCP is for the removal of ductal stones (predominantly CBD stones).
- Magnetic resonance cholangiopancreatography (MRCP)
 - The presence of a CBD calculus should be confirmed prior to subjecting the patient to a potentially dangerous procedure such as an ERCP - MRCP would be the most appropriate test to do this.
 - > the most sensitive for a diagnosis of gallstones
 - In terms of sensitivity for determining the presence of stones anywhere within the biliary tract, MRCP and EUS would be the most sensitive investigations with little to choose between them (ERCP may well miss small stones in the gallbladder).

Management

- In patients with <u>severe gallstone pancreatitis</u> → ERCP and endoscopic stone extraction should be performed within 72 hours of the onset of pain.
- In patients with **mild gallstone pancreatitis**, in the absence of cholangitis, there is no evidence to support ERCP and stone extraction in the acute setting; however arrangements

must be made for definitive management of common bile duct stones on the same admission or within two weeks of recovery.

- Asymptomatic gallstones which are located in the gallbladder are common and do not require treatment.
- However, if stones are present in the common bile duct there is an increased risk of complications such as cholangitis or pancreatitis and surgical management should be considered.
- endoscopic retrograde cholangiopancreatography (ERCP) for biliary sphincterotomy and stone extraction.
 - the most common procedure-related complication is → Pancreatitis
 - risks of developing this complication:
 - Female sex,
 - ❖ age less than 60 and
 - a low probability of structural disease (suggested by a normal bilirubin, non-dilated ducts or suspected sphincter of Oddi dysfunction)
- Percutaneous transhepatic cholangiography is an interventional radiological procedure which is generally reserved for therapeutic decompression of an obstructed biliary system where ERCP is unsuccessful or not possible.

Complications

- Cholecystitis
- Acute pancreatitis
- Gallbladder cancer
- · Choledocolithiasis
 - calculi in the common bile duct
- · Fistula between gallbladder and small intestine
 - passed gallstone can obstruct the ileocecal valve

Glasgow score for Pancreatitis:

- 1. PaO₂ <7.29 kPa
- 2. Glucose >10 mmol/L
- 3. Age >55 years
- 4. WBC >15
- 5. Calcium < 2.0 mmol/L
- 6. Urea >16 mmol/L
- 7. LDH >600 IU/L
- 8. Albumin <32 g/L

Interpretation of glasgow score for pancreatitis:

- The presence of **three or more** of these criteria within the first 48 hours is indicative of **severe pancreatitis.**
- If the score ≥3, severe pancreatitis is likely Referral to the HDU/ICU is suggested in this case. If the score <3, severe pancreatitis is unlikely.

Functional gall bladder pain

- The Rome III criteria for functional gall bladder pain are as follows:
 - episodes lasting 30 minutes or longer
 - recurrent symptoms occurring at different intervals (not daily)
 - the pain builds up to a steady level
 - the pain is moderate to severe enough to interrupt the patient's daily activities or lead to an Emergency Department visit
 - the pain is not relieved by bowel movements

- the pain is not relieved by postural change
- > the pain is not relieved by antacids, and
- exclusion of other structural disease that would explain the symptoms.
- The pain may present with one or more of the following supportive criteria:
 - associated with nausea and vomiting
 - radiates to the back and/or right infra subscapular region, and
 - awakens from sleep in the middle of the night.

Choledochal cysts

- · Choledochal cysts are congenital bile duct anomalies, cystic dilatations of the biliary tree
- The classic triad in adults with choledochal cysts is:
 - 1. abdominal pain, (Most common symptom)
 - 2. jaundice, and
 - 3. palpable right upper quadrant abdominal mass.
 - ➤ However, this triad is found in only 10-20% of patients.
- Adults may present with complications (eg, hepatic abscesses, cirrhosis, portal hypertension, recurrent pancreatitis, cholelithiasis)
- Abdominal ultrasonography is the investigation of choice
- Choledochal cysts are usually diagnosed in the neonatal period but a few are delayed until adulthood. The Todani classification is used to define these:
 - Type 1 a fusiform dilation of the common hepatic duct (CHD) the most common
 - > Type 2 a diverticulum of the CHD
 - > Type 3 a choledochcele
 - > Type 4 describes extension into the intrahepatic ducts (the second most common)
 - > Type 5 intrahepatic cystic disease only.
- Treatment
 - Resection and reconstruction is advised to prevent recurrent cholangitis, pancreatitis, and malignant change.

Sphincter of Oddi dysfunction

- Type 1 Sphincter of Oddi dysfunction (SOD) is characterised by:
 - abdominal pain,
 - deranged liver function tests.
 - > a dilated biliary tree without strictures, and
 - delayed emptying of contrast at ERCP.
 - Delayed excretion of contrast is definitive and Sphincter of Oddi manometry need not be carried out with this finding.
- Type 2 SOD
 - pain with only one or two other criteria from the type 1 definition
- type 3 SOD
 - biliary type pain only.
 - ➤ Diagnosis in type 3 is supported by abnormal manometry although this will only be present in 12-28% of these patients so the diagnosis is most often one of exclusion.

Post-cholecystectomy syndrome

- Post-cholecystectomy syndrome is a recognised complication of cholecystectomies.
- Typically, symptoms of dyspepsia, vomiting, pain, flatulence and diarrhoea occur in up to 40% patients post-surgery.
- The pathology behind the syndrome isn't completely clear, however there is some association with remnant stones and biliary injury.
- Pain is often due to sphincter of Oddi dysfunction and the development of surgical adhesions.
- · Management:
 - low-fat diet
 - > bile acid sequestrants, such as Cholestyramine, to bind the excess bile acids and thus preventing lower gastrointestinal signs.
 - Proton-pump inhibitors like Lansoprazole do play a role, if the patient is complaining of dyspeptic like symptoms.

Bile-acid malabsorption

SeHCAT is the investigation of choice for bile acid malabsorption

- Although a small proportion of bile acids (3%) are excreted in the faeces, about 97% of bile acids are recycled.
- Bile-acid malabsorption is a cause of chronic diarrhoea.
 - ➤ the bile, with no gall bladder to store it, is excreted directly into the gut → diarrhoea
- In people with bile acid malabsorption, excess bile in the colon stimulates electrolyte and water secretion, which results in chronic watery diarrhoea.
- May affect 10% of patients following cholecystectomy.
- Typically it is post-prandial
- There is evidence suggesting that up to one-third of people with a diagnosis of IBS with diarrhoea (IBS-D) have bile acid malabsorption

mechanisms

- Bile acid malabsorption causes diarrhoea by 1 of the following mechanisms:
 - > inducing secretion of sodium and water increasing colonic motility
 - > stimulating defecation
 - > inducing mucus secretion
 - > damaging the mucosa, thereby increasing mucosal permeability.

Types: divided into 3 types depending on aetiology:

- type 1: following ileal resection, disease or bypass of the terminal ileum
- type 2: primary idiopathic malabsorption
- type 3: associated with cholecystectomy, peptic ulcer surgery, chronic pancreatitis, coeliac disease or diabetes mellitus.

Causes:

- 1. Primary: due to an excessive production of bile acid,
- Secondary: Due to an underlying gastrointestinal disorder, causing reduced bile acid absorption
 - often seen in patients with ileal disease, such as with Crohn's.
 - > cholecystectomy
 - coeliac disease

- > small intestinal bacterial overgrowth
- Ileal resection
- > drugs:
 - Biguanides (metformin) ,
 - Colchicine, used for treating gout in patients where (NSAIDs) are contraindicated

Investigation

- the test of choice is SeHCAT
 - nuclear medicine test using a gamma-emitting selenium molecule in selenium homocholic acid taurine or tauroselcholic acid (SeHCAT) (⁷⁵Selenium HomotauroCholic Acid Test)
 - scans are done 7 days apart to assess the retention/loss of radiolabelled⁷⁵SeHCAT
 - Retention values of less than 15% have been considered abnormal and indicative of bile acid malabsorption.
 - ❖ retention values of 10–15% (mild bile acid malabsorption)
 - * retention values of 5–10% (moderate bile acid malabsorption)
 - * retention values of 0–5% (severe bile acid malabsorption).

Management

· bile acid sequestrants e.g. cholestyramine

Primary biliary cirrhosis

Primary biliary cirrhosis - the M rule

- IgM
- anti-Mitochondrial antibodies, M2 subtype
- Middle aged females

Aetiology

· autoimmune condition.

Mechanism

chronic inflammatory process → damage to interlobular bile ducts → cholestasis & cirrhosis.

Epidemiology

female: male ratio → 9:1

Associations

- Sjogren's syndrome (seen in up to 80% of patients)
- · rheumatoid arthritis
- · systemic sclerosis
- thyroid disease

Clinical features

The two main conditions causing **pigmentation** and **chronic liver disease** are:

- 1. primary biliary cirrhosis (PBC) and
- 2. Haemochromatosis.
- early: may be asymptomatic (e.g. raised ALP on routine LFTs) or fatigue, pruritus
 - ➤ classic presentation → itching in a middle-aged woman
- cholestatic jaundice
- hyperpigmentation, especially over pressure points
- · xanthelasmas, xanthomata
- · also: clubbing, hepatosplenomegaly
- Fat malabsorption leading to deficiency of the vitamins A, D, E, K (hence osteomalacia and also bruising).
- Back pain

- due to osteomalacia resulting from malabsorption or osteoporosis hepatic osteodystrophy.
- · late: may progress to liver failure

Diagnosis

- anti-mitochondrial antibodies (AMA) M2 subtype are present in 98% of patients and are highly specific
 - > (AMAs) targeted against pyruvate dehydrogenase.
 - Pyruvate dehydrogenase (PD) is found in the mitochondria. required for the generation of acetyl-CoA from pyruvate for entry into the tricarboxylic acid (TCA) cycle.
- · smooth muscle antibodies in 30% of patients
- raised serum IgM
- · Liver function tests
 - LFT correlate poorly with histology in PBC the disease may progress insidiously with normal or near-normal LFTs.

Complications

- malabsorption: osteomalacia, coagulopathy
- Osteoporosis is a common complication, possibly due to vitamin D malabsorption and/or premature ovarian failure. All patients with PBC should be screened for the condition → The patient should undergo bone mineral densitometry.
- sicca syndrome occurs in 70% of cases
- portal hypertension: ascites, variceal haemorrhage
- hepatocellular cancer (20-fold increased risk)

Management

- · pruritus: cholestyramine
- fat-soluble vitamin supplementation
- ursodeoxycholic acid (UDCA)
 - > UDCA delays the need for liver transplantation
 - > improves liver biochemistry and may slow disease progression.
 - The effectiveness of UDCA is monitored by improvements in ALP and GGT, but ALP is more widely used than GGT.
- liver transplantation
 - > e.g. if bilirubin > 100 (PBC is a major indication)
 - ➤ Liver transplantation has a good prognosis (90–95% survival)
 - > recurrence in graft can occur but is not usually a problem
 - occur in 10% to 40% of patients
 - but recurrent PBC does not affect either graft or patient survival rates.
 - > contraindication to liver transplantation:
 - Psychological factors that may impair compliance with immunosuppression

Primary sclerosing cholangitis (PSC)

4% of patients with UC have PSC, 80% of patients with PSC have UC

Definition

 Primary sclerosing cholangitis is a biliary disease of unknown aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts

Epidemiology

- Sex: ♂ > ♀ (2:1)
- Age: The median age at diagnosis is ~ 40.
- primarily seen in middle-aged men with inflammatory bowel disease.

Associations

- ulcerative colitis: 4% of patients with UC have PSC, 80% of patients with PSC have UC
- Crohn's (much less common association than UC)
- HIV/

If a patient with pre-existing chronic inflammatory bowel disease displays increased ALP, GGT, and conjugated bilirubin, always consider PSC

Features

- asymptomatic
 - > 50 % of patients
- <u>cholestasis</u>: (alkaline phosphatase greater than transaminases) → jaundice and pruritus
 conjugated hyperbilirubinemia.
- · right upper quadrant pain
- fatigue
- intermittent diarrhoea.

Investigation

- MRCP (Magnetic resonance cholangiopancreatography)
 - Non-invasive, often performed initially.
 - > the initial diagnostic investigation of choice
- ERCP
 - the standard diagnostic tool,
 - More invasive but also more accurate than MRCP
 - Good alternative for patients who cannot undergo MRI testing (e.g., patients with pacemaker)
 - showing multiple biliary strictures giving a 'beaded' appearance
- Antibodies:
 - ANCA may be positive (pANCA 84%, aCL 66%, , and ANA 53%)
- IgM →increased (hypergammaglobulinaemia)
- Liver biopsy
 - there is a limited role for liver biopsy,
 - > may show fibrous, obliterative cholangitis often described as 'onion skin'

Complications

- cholangiocarcinoma (in 10%)
- · increased risk of colorectal cancer
- PSC → ↓ secretion of bile acids; → steatorrhea → ↓ fat-soluble vitamins → Night blindness

Treatment

Liver transplant is the definitive treatment

Prognosis

• The median time to liver failure around 12 years.

Differential diagnoses of primary cholangitis			
	Primary sclerosing cholangitis	Primary biliary cholangitis	
Epidemiology	More common among middle-aged men	More common among middle-aged women	
Pathophysiology	Progressive chronic inflammation of both intrahepatic and extrahepatic bile ducts	Progressive destruction of only intrahepatic small and medium-sized bile ducts	
Antibodies	pANCA	Anti-mitochondrial antibodies (AMA)	
Complications	Associated with cholangiocarcinoma and ulcerative colitis	Associated with autoimmune conditions	

Cholangiocarcinoma

- The vast majority of cholangiocarcinomas (70%) are sporadic.
- Risk factors:
 - Primary sclerosing cholangitis (PSC) is the most common risk factor
 - Others
 - diabetes
 - fatty liver disease, and
 - inflammatory bowel disease without PSC.
 - Alcohol
 - Smoking
 - Chronic hepatitis B
 - obesity
- The imaging characteristics of a cholangiocarcinoma are hypovascularity with scarring and calcification.
 - CT contrast is delivered in early (hepatic arterial) phase and delayed (portal venous) phase
 - 80% of normal liver tissue derives its blood supply from the portal vein, but tumours generally derive their blood supply from the hepatic artery and are therefore hypervascular.
 - Cholangiocarcinomas are an exception as hypovascular lesions.
- The Bismuth-Corlette classification is as follows:
 - > Type I below confluence of left and right hepatic ducts
 - > Type II reaching confluence but not involving left or right hepatic ducts
 - Type III occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct

Liver conditions

Hepatomegaly

Common causes of hepatomegaly

- Cirrhosis: if early disease, later liver decreases in size. Associated with a non-tender, firm liver
- Malignancy: metastatic spread or primary hepatoma. Associated with a hard, irregular. liver edge
- Right heart failure: firm, smooth, tender liver edge. May be pulsatile

Other causes

- viral hepatitis
- glandular fever
- malaria
- abscess: pyogenic, amoebic
- hydatid disease

- · haematological malignancies
- haemochromatosis
- · primary biliary cirrhosis
- sarcoidosis, amyloidosis

Hepatosplenomegaly

Causes of hepatosplenomegaly

- chronic liver disease* with portal hypertension
- · infections: glandular fever, malaria, hepatitis
- · lymphoproliferative disorders
- myeloproliferative disorders e.g. CML
- amyloidosis

<u>Gaucher's disease</u> is a lysosomal storage disease, <u>due to deficiency of the lysosomal hydrolase beta-glucosidase</u>. most commonly seen in Ashkenazi Jews. Its features include hepatosplenomegaly, haematological abnormalities and skeletal involvement.

Liver function test

- Gamma-glutamyl-transferase (GGT)
 - → ↑↑ by drugs such as phenytoin and alcohol.
 - Mild raises in GGT can occur with any alcohol intake, and a rise does not always indicate liver pathology.
 - > ↑↑ in fatty liver
- Transaminase
 - differential diagnosis for elevated serum aminotransferases:
 - · viral hepatitis,
 - hepatotoxicity from drugs or toxins,
 - alcoholic liver disease,
 - hepatic ischemia, and
 - malignant infiltration
 - Only ischaemic hepatitis and paracetamol overdose tend to produce transaminase levels that are raised to very high degree (more than 100 times the upper limit of normal).
 - hypotension (particularly in an individual who is normally hypertensive) is the usual precipitant for ischaemic hepatitis.

^{*}the latter stages of cirrhosis are associated with a small liver

- > Remember that the level to which transaminases are elevated cannot be used to judge the degree of liver damage and impairment of hepatic function.
- Patients with a hepatocellular process generally have a disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase, while those with a cholestatic process have the opposite findings.
- AST/ALT ratio:
 - fatty liver: AST/ALT usually <1
 - alcohol abuse: AST/ALT ratio >2:1

Alkaline phosphatase (ALP)

- Causes of raised (ALP):
 - liver: cholestasis, hepatitis, fatty liver, neoplasia
 - In cholestasis, ALP is typically elevated to at least four times the upper limit of normal.
 - ⇒ Lesser degrees of elevation are nonspecific and may be seen in other liver diseases
 - Paget's
 - osteomalacia
 - bone metastases
 - hyperparathyroidism
 - renal failure
 - physiological: pregnancy, growing children, healing fractures

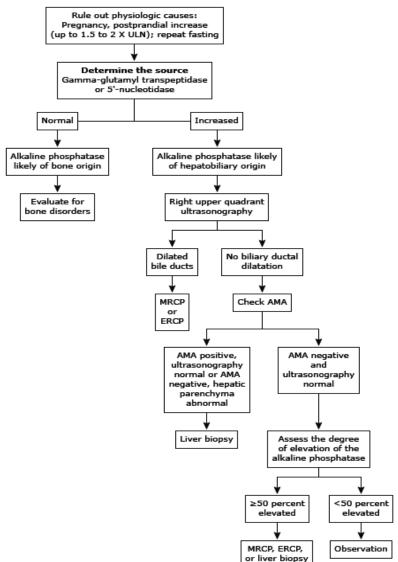
The table below splits the causes according to the calcium level

Raised ALP and raised calcium	Raised ALP and low calcium
Bone metastases Hyperparathyroidism	Osteomalacia Renal failure

↑ALP → do ultrasonography:

- presence of biliary dilatation → extrahepatic cholestasis (gallstones, strictures, or malignancy).
- absence of biliary dilatation → intrahepatic cholestasis (drug toxicity, primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, cholestasis of pregnancy, benign postoperative cholestasis, infiltrative diseases, and total parenteral nutrition).

Evaluation of elevated serum alkaline phosphatase (2019 UpToDate)



AMA: antimitochondrial antibodies; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; ULN: upper limit of normal.

Liver biopsy

Contraindications to percutaneous liver biopsy

- deranged clotting (e.g. INR > 1.4)
 - Percutaneous liver biopsy should be avoided if the INR is greater than 1.3 (prothrombin time greater than three seconds above normal).
 - If the INR is >1.4, fresh frozen plasma (FFP) may be administered and liver biopsy then carried out if the INR is less than 1.4.
- low platelets (e.g. < 60 * 10⁹/l)
 - > The minimum safe lower limit of platelets is 60.
 - Where the platelet count is 40-60 biopsy can be performed immediately after platelet transfusion provided there has been an increment to the recommended level.
- Anti-platelet medication
 - > should be stopped for at least one week prior to liver biopsy.
- anaemia
- extrahepatic biliary obstruction
- hydatid cyst
- haemoangioma
- uncooperative patient
- ascites
 - Significant volume ascites is a contraindication to percutaneous liver biopsy but a trans-jugular biopsy can be performed as an alternative.

Acute liver failure

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

Causes

- · paracetamol overdose
- alcohol
- · viral hepatitis (usually A or B)
- acute fatty liver of pregnancy

Features*

- · jaundice
- · coagulopathy: raised prothrombin time
- hypoalbuminaemia
- hepatic encephalopathy
- renal failure is common ('hepatorenal syndrome')

Note:

 *remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver. This is best assessed by looking at the prothrombin time and albumin level.

Ascites

Causes

- The serum ascites albumin gradient (SAAG) is the most sensitive and specific method of categorising ascites.
 - > To calculate the ascitic fluid albumin should be subtracted from the serum albumin.
 - A value that is ≥11 g/L (high SAAG) indicates a transudate (e.g. cirrhosis, cardiac failure),
 - <11 g/L (low SAAG) indicates an exudate (e.g. malignancy, pancreatitis).</p>
- The causes of ascites can be grouped into those with a serum-ascites albumin gradient (SAAG) <11 g/L or a gradient >11g/L as per the table below:

SAAG > 11g/L	SAAG <11g/L
Cirrhosis Alcoholic hepatitis Cardiac ascites Mixed ascites Massive liver metastases Fulminant hepatic failure Budd-Chiari syndrome Portal vein thrombosis Veno-occlusive disease Myxoedema Fatty liver of pregnancy	Peritoneal carcinomatosis Tuberculous peritonitis Pancreatic ascites Bowel obstruction Biliary ascites Post operative lymphatic leak Serositis in connective tissue diseases

Characteristics of ascitic fluid

- Causes of a transudate (protein < 30 g/l, assuming a normal albumin level):
 - Hepatic cirrhosis
 - > Right-sided cardiac failure
 - Hypoalbuminaemia (nephrotic syndrome)
 - > Acute nephritis
 - > Budd-Chiari syndrome
- Causes of an exudate (protein > 30 g/l):
 - Infection (tuberculosis, peritonitis)
 - Inflammation (vasculitis)
 - Malignancy
 - > inhaler.

Treatment

- Large, symptomatic ascites → therapeutic paracentesis.
 - Several large randomised, controlled trials have shown that repeated large volume paracentesis (4-6 L) is safer and more effective for the treatment of tense ascites compared with larger than usual doses of diuretics.
 - > Paracentesis is relatively contraindicated if the patient is encephalopathic,
 - Paracentesis is less likely to be successful if the patient has peripheral oedema
 - Whilst therapeutic paracentesis will be necessary in light of the large volume tense ascites it would be advisable to consider doing this with FFP cover.
- Not large, asymptomatic ascites → dietary salt restriction (to no more than 90 mmol/day) + spironolactone.
 - > The initial management would be spironolactone
 - Initial dose of spironolactone is 100 mg/day and may be titrated up to 400 mg/day.
 - Once the maximum dose of spironolactone has been reached furosemide can be added if there is still significant ascites accumulation and the renal function and electrolytes will tolerate further diuresis.
 - Doses of furosemide are advised start at 40 mg/day titrating up to 160 mg/day as tolerated or needed.
 - > Furosemide alone has poor efficacy in cirrhosis.
 - A major reason for so-called diuretic-resistant ascites is an excess sodium intake,
 - no-added salt diet is recommended for all patients with ascites secondary to chronic liver disease.
 - Spironolactone is more effective than furosemide <u>because</u> the site of sodium retention in cirrhosis is the distal nephron
 - The ideal weight loss is 0.5 kg/day, as any more than this may cause cardiovascular strain.

- transcutaneous liver biopsy is contraindicated with ascites (use transjugular biopsy if absolutely necessary).
- Management of hyponatraemia in patients with chronic liver disease and ascites:
 - ➤ serum sodium is 126-135 mmol/L → No specific intervention other than monitoring
 - ➤ serum sodium is 121-125 mmol/L + normal creatinine → Reduce diuretics
 - ➤ serum sodium is 121-125 mmol/L + high creatinine → Stop diuretics + give volume expansion
 - > serum sodium is ≤120 mmol/L → Stop diuretics + give volume expansion with colloid or normal saline.
- Management of hypoproteinemia in patients with chronic liver disease
 - Cirrhotic ascites has significantly lower protein and complement levels than noncirrhotic ascites.
 - This can result in less opsonic activity of the peritoneal fluid predisposing to spontaneous bacterial peritonitis.
 - > indications for the use of albumin in cirrhosis:
 - post-paracentesis circulatory dysfunction,
 - spontaneous bacterial peritonitis, and
 - hepatorenal syndrome.
 - Albumin replacement treatment is warranted in this diagnosis and can also decrease the development of the hepatorenal syndrome.
 - > 20% salt poor albumin (human albumin solution)
 - The salt-poor preparation of albumin is particularly important in this scenario as high salt load will encourage fluid to shift into the extravascular compartment resulting in fluid overload.

What is the most characteristic physiological activity that retains sodium in the face of salt and water overload?

- → Arterial underfilling
 - In liver cirrhosis, arterial vasodilatation due to nitric oxide overactivity, coupled with hypoalbuminemia, which drives low colloid osmotic pressure, leads to arterial underfilling.

Meig's syndrome → ovarian fibroma associated with a pleural effusion and ascites

Complications of cirrhosis	Albumin use	
PPCD	8 g/l of ascites removed (above 5 l)	
SBP	1.5 g/kg on day 1 and 1g/kg on day 3 (in association with antibiotics)	
HRS	Loading and maintenance dose + terlipressin untill HRS resolution	
Non-SBP Infections	Improvement in renal and circulatory function (no effect on survival, only one study available)	tions ed)
НЕ	Only two discordant studies available (effect on oxidative stress)	rersial indication studies needed
Ascites	(no effect on survival, only one study available) Only two discordant studies available (effect on oxidative stress) Not yet enough evidence for the utility of chronic use (ANSWER Study currently ongoing)	
ACLF	Albumin dialysis (MARS and Prometheus systems)	

Summary table of the current uses of albumin in hepatology, according to the main international guidelines and looking at future perspectives (**PPCD**: post-paracentesis circulatory dysfunction; **SBP**: spontaneous bacterial peritonitis; **HRS**: hepatorenal syndrome; **HE**: hepatic encephalopathy; **ACLF**: acute-on-chronic liver failure).

Liver cirrhosis

Pathophysiology

- which hepatic cells are central to the process of fibrosis?
 - The hepatic stellate cells are central to the process of fibrosis within the liver.
- What is the pro-inflammatory factor in fibrotic liver injury which activate the stellate cells?
 - > Tumour necrosis factor-a is a pro-inflammatory effector in fibrotic liver injury, through activation of the stellate cells. These cells then secrete the fibrillar collagen constituting the defining features of hepatic fibrosis.
 - ➤ Interleukin-10 is thought to exert anti-inflammatory effects on the stellate cell.
- Which mediator is released by stellate cells that causes fibrosis seen in cirrhosis?.
 - Transforming growth factor-beta is the mediator released by stellate cells that causes fibrosis
- Which factor that causing contraction of the hepatic stellate cells?
 - Endothelin is a vasoconstrictor in the hepatic sinusoids (similarly in the endothelium of the systemic circulation) and functions by causing contraction of the hepatic stellate cells thus increasing intrahepatic sinusoidal resistance and promoting portal hypertension.
 - Nitric oxide antagonises the effects of endothelin in the liver.
- Pathogenesis includes the replacement of type IV collagen in the perisinusoidal space (space of Disse) with type I and III collagen.

Features

- Cardiac
 - Cardiac output is often elevated
 - The cardiomyopathy of alcoholism is a dilated or congestive form.

Dilated cardiomyopathy

- hyperdynamic circulation
- > systemic vasodilatation
- ↓↓ vascular resistance,
- ➤ increased plasma volume → low serum sodium.
 - Most patients have sodium and water retention.
 - Secondary hyperaldosteronism will result in total body sodium overload but not necessarily hypernatraemia.
 - Remember that the sodium level is a concentration, therefore if the amount of solvent (water) is increased then it will not necessarily rise.

Abdominal symptoms

- Hepatomegaly (possibly causing RUQ pain)
- Splenomegaly
- Ascites
- Portal hypertension
 - Hepatic intrasinusoidal pressure is elevated
 - Which features is most indicative of decompensated portal hypertension?
 - ⇒ Caput medusae
- Which sign is a direct result of decreased hepatic oncotic function in cirrhotic patients?
 - Lower limb swelling
- Hormone disorders
 - Hyperestrogenism
 - Gynecomastia, decreased body hair (e.g., chest hair)
 - Gynaecomastia
 - ⇒ What is the cause of gynaecomastia in cirrhosis?
 - Altered oestrogen metabolism
 - * ↓↓ metabolism of sex steroids → ↑↑ oestrogen level.
 - there is associated testicular atrophy and loss of body hair.
 - May occur as a result of spironolactone therapy (an aldosterone antagonist).
 - Hypogonadism (testicular atrophy)
 - Reduced libido, erectile dysfunction, infertility
 - > Amenorrhea

Why do patients get oedema in liver disease?

- 1. Low albumin
- 2. Stimulation of RAAS leads to fluid retention

Classifications

- Child-Pugh classification of liver cirrhosis
 - The Child-Pugh classification is a scoring system to assess the severity of liver cirrhosis

Score	1	2	3
Bilirubin (m mol/l)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
Prothrombin	<4	4-6	>6

Score	1	2	3
time, prolonged by (s)			
Encephalopathy	None	mild	marked
Ascites	None	mild	marked

- Summation of the scores allows the severity to be graded either A, B or C:

 - ❖ 7-9 = B
 - ◆ 9 = C
- Cirrhosis can be micro- or macronodular in type.
 - micronodular form: the nodules are less than 3 mm across with uniform liver involvement - seen in alcohol or biliary disease.
 - macronodular form: there are larger nodules, classically seen in chronic viral hepatitis.

Investigations

- ALT is more specific than other liver enzymes in diagnosing hepatic injury.
- the most important immediate investigation for patient with hepatic cirrhosis presented in a confused and drowsy state → Blood glucose (hepatic gluconeogenesis can be significantly down-regulated)
- ↑↑ plasma volume
- 🔟 serum sodium
 - > Patients with cirrhosis are frequently hyponatraemic.
 - This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).
- Urinary sodium concentration is usually less than 10 mmol/l
 - Reduced urinary sodium excretion
 - Patients with cirrhosis are frequently hyponatraemic. This is a function of an inability to excrete free water (increased ADH levels and systemic vasodilation contribute, but the underlying mechanism is complex and not entirely understood).

Thrombocytopenia is a common finding in chronic liver disease.

Sex hormones in liver cirrhosis

- Clinical features of male cirrhotic subjects are feminization(gynecomastia etc) and hypogonadism(testicular atrophy, reduced fertility, loss of libido, impotence etc).
- sex hormones
 - decrease in serum testosterone levels
 - > increase in serum estrogen levels
 - increase in ratio of estrogen to testosterone
 - Hyperestrogenization may be related with feminization of male cirrhotic subjects, whereas hypogonadism is the result of alcohol abuse per se, rather than the indirect consequence of liver cirrhosis.

What are the causes of decompensation in liver disease

- Infection
- · Spontaneous bacterial peritonitis
- · GI bleeding
- Sedatives
- HCC

Prognosis

• Five-year survival after liver transplantation is now 75%.

Liver transplant

Guidelines for referral to a liver unit following paracetamol overdose include

- Metabolic acidosis (pH <7.3 or bicarbonate <18 mmol/L).
- INR >3 (or prothrombin time >50 seconds)
 - > INR >2.0 at or before 48 hours or >3.5 at or before 72 hours should prompt referral to a specialist unit.
 - > Peak elevation occurs around 72-96 hours.
- Oliquria
- Creatinine >200 µmol/L,
 - (use haemodialysis if >400 µmol/L)
- Hypoglycaemia.
- Systolic BP <80 mm Hg despite adequate fluid resuscitation
- Any degree of encephalopathy 48 hours after ingestion.
- raised intracranial pressure (ICP)
 - > signs of CNS oedema include:
 - BP >160/90 mmHg (sustained) or brief rises (systolic >200 mmHg),
 - bradvcardia.
 - decerebrate posture,
 - extensor spasms, and
 - poor pupil responses

Criteria for liver transplant in fulminant failure in cases of paracetamol overdose include:

- arterial pH lower than 7.3 or
- all of the following:
 - > Prothrombin time greater than 100 seconds
 - > Creatinine greater than 300 µmol/L, and
 - Grade 3-4 encephalopathy.

Criteria for liver transplant in fulminant failure in non-paracetamol cases include:

- INR greater than 6.7 or
- prothrombin time greater than 100 seconds, or
- · any three of the following:
 - > Aetiology that is not due to hepatitis A, hepatitis B or a drug reaction
 - > Age less than 10 years or more than 40 years
 - > Jaundice more than seven days before encephalopathy
 - > INR greater than 4 or prothrombin time greater than 50 seconds, and
 - Bilirubin greater than 300 μmol/L.

When referral/discussion with the liver transplant unit is required for a patient with acute liver failure?		
Paracetamol induced acute liver failure	Non-paracetamol induced acute liver failure	
➤ Arterial pH < 7.30 or HCO3 <18 ➤ INR>3.0 on day two or > 4.0 thereafter. ➤ Oliguria and/or AKI ➤ Altered level of consciousness ➤ Hypoglycaemia ➤ Elevated arterial lactate (>4mmol/L) unresponsive to fluid resuscitation	 ▶ pH < 7.30 , or HCO3 < 18mmol/l ▶ INR >1.8 ▶ Oliguria/renal failure or Na < 130mmol/L ▶ Encephalopathy, hypoglycaemia or metabolic acidosis ▶ Bilirubin >300 umol/L (17.6mg/dL) 	

Ref: Adult liver transplantation: A UK clinical guideline. March 2020. www.bsg.org.uk (PassOnExam)

Portal hypertension

Basics

• The liver receives approximately 1500 ml of blood each minute, two-thirds of which is provided by the portal vein.

Definition:

- abnormally high pressure in the hepatic portal vein (hepatic venous pressure gradient of 10 mm Hg or more).
- Portal hypertension is present when the wedged hepatic vein pressure is more than 5 mmHg higher than the inferior vena cava pressure.

Mechanism of porto-systemic collaterals

- Because the veins in the portal system lack valves, increased resistance to flow at any
 point between the splanchnic venules and the heart will increase the pressure in all vessels
 on the intestine site of the obstruction.
- This is manifest clinically by the development of porto-systemic collaterals (oesophageal varices), splenomegaly and/or ascites.

Site of Anastomosis	Clinical Sign	Portal ↔ Systemic
Esophagus	Esophageal varices	Left gastric ↔ esophageal
Umbilicus		Paraumbilical ↔ superficial and inferior epigastric
Rectum		Superior rectal ↔ middle and inferior rectal

Causes: (Vascular resistance and blood flow are 2 important factors in its development).

- Pre-hepatic (pre-sinusoidal) blockage of the portal vein before the liver
 - Congenital atresia or stenosis.
 - Portal vein thrombosis (idiopathic, umbilical and portal sepsis, malignancy, hypercoagulable states, pancreatitis).
 - Longstanding portal vein thrombosis is a well recognised complication in premature neonates due to cannulation of the umbilical vein during neonatal intensive care.
 - ❖ the best initial investigation is → Ultrasound with Doppler
 - > Splenic vein thrombosis.
 - > Extrinsic compression eq. tumours.
- Hepatic (sinusoidal)
 - Cirrhosis. (the most common cause)
 - Chronic hepatitis.
 - > Schistosomiasis.
 - Myeloproliferative diseases.
 - Idiopathic portal hypertension.
 - Granulomata eg, sarcoid.
 - Nodular (nodular regenerative hyperplasia, partial nodular transformation).
 - Toxins (arsenic, vinyl chloride).
 - Fibropolycystic disease (including congenital hepatic fibrosis).
 - Post-hepatic (post-sinusoidal) blockage of hepatic veins or venules
 - > Budd-Chiari syndrome (hepatic vein obstruction).
 - Constrictive pericarditis.
 - Right heart failure.
 - Veno-occlusive disease of the smaller hepatic veins/venules (due to ingestion of pyrrolizidine alkaloids; antileukaemic drugs, radiation).
 - > Sclerosing hyaline necrosis.

Portal hypertension measurement:

- Portal pressure is indirectly measured in clinical practice by the hepatic venous pressure gradient (HVPG).
- The HVPG is calculated by subtracting the free hepatic venous pressure (which reflects intraabdominal pressure) from the wedged hepatic venous pressure (which reflects portal venous pressure). These values are obtained by hepatic venous catheterization.
- Normal HVPG values are <5 mm Hg.
- HVPG >10 mm Hg predicts the development of oesophageal varices.
- However, HVPG is moderately invasive and its clinical role is uncertain.
- The normal hepatic venous pressure gradient (normal HVPG = 1-5 mmHg) means that the portal hypertension is not related to post-sinusoidal intrinsic liver disease such as cirrhosis

- (caused in children by metabolic disorders such as A1ATD) or post-hepatic venous obstruction (HV thrombosis).
- The haemodynamic goal of treatment is reduce the HVPG by 20% or to less than 12 mmHg, using a non-selective beta blocker. If this is not achievable despite titrating the beta-blocker dose, then endoscopic variceal ligation must be considered.
- · Wedged hepatic venous pressure
 - > the pressure recorded by a catheter wedged in a hepatic vein. It reflects the portal venous pressure in the hepatic sinusoids.
 - ➤ ↑↑ in sinusoidal and post-sinusoidal portal hypertension,
 - remains normal in pre-sinusoidal portal hypertension.

Complications of portal hypertension:

- · Haematemesis or melaena suggest bleeding varices.
- Lethargy, irritability and changes in sleep pattern suggest encephalopathy.
- · Increased abdominal girth, weight gain suggest ascites.
- Abdominal pain and fever suggest spontaneous bacterial peritonitis.
- Pulmonary involvement is common in patients with portal hypertension

Trans-jugular intrahepatic porto-systemic shunt (TIPSS)

- Indications are:
 - Diuretic resistant ascites (Intractable ascites)
 - Intractable portal hypertensive bleeding and
 - Hepato-renal failure.
- contraindications to shunting:
 - Severe hepatic encephalopathy
 - > Severe heart failure
 - Septicaemia

Hepatic encephalopathy

- Hepatic encephalopathy may be seen in liver disease of any cause.
- The aetiology is not fully understood but is thought to include excess absorption of ammonia from bacterial breakdown of proteins in the gut

Features

- confusion, altered GCS (see below)
- hepatic flap
 - > Asterixis (also called the flapping tremor, or liver flap) is a tremor of the hand when the wrist is extended, sometimes said to resemble a bird flapping its wings.
 - hepatic encephalopathy is unlikely to be present if a liver flap (asterixis) cannot be detected.
- constructional apraxia: inability to draw a 5-pointed star
- triphasic slow waves on EEG
- raised ammonia level (not commonly measured anymore)

Grading of hepatic encephalopathy

- Grade I: mood changes like depression or irritability, and sleep abnormalities (typically sleep inversion)
- · Grade II: Confusion, inappropriate behaviour
- · Grade III: Incoherent, restless

· Grade IV: Coma

Precipitating factors

- · infection e.g. spontaneous bacterial peritonitis
- GI bleed
- constipation
- · drugs: sedatives, diuretics
- hypokalaemia
- · renal failure
- increased dietary protein (uncommon)

Treatment

- Treat precipitating cause (e.g., give K+ if hypokalemic)
- Lactulose
 - metabolized to lactic acid by colonic flora, converts NH₃ to NH₄+ which can be absorbed
- Neomycin
 - replaced with rifamixin, neomycin no longer routinely used
 - > antibiotics kill colonic flora leading to decreased NH₃ production

Hepatorenal syndrome (HRS)

Hepatorenal syndrome is primarily caused by splanchnic vasodilation

Pathophysiology

vasoactive mediators cause → splanchnic vasodilation → ↓↓ systemic vascular resistance → 'underfilling' of the kidneys → activation of the renin-angiotensin-aldosterone system by the juxtaglomerular apparatus → renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation.

Types

Hepatorenal syndrome has been categorized into two types:

Type 1 HRS	Type 2 HRS	
 Rapidly progressive Doubling of serum creatinine to > 221 mmol/L or a halving of the creatinine clearance to less than 20 ml/min over a period of less than 2 weeks Very poor prognosis 	 Slowly progressive characterised by a moderate and stable reduction in renal function, hypotension and diuretic resistance. Prognosis poor, but patients may live for longer 	

Management

- The ideal treatment is liver transplantation, but patients are often too unwell to have surgery and there is a shortage of donors
- Other Management options
 - ➤ agonists of vasopressin V1 receptors such as terlipressin → vasoconstriction of the splanchnic circulation
 - volume expansion with 20% albumin
 - transjugular intrahepatic portosystemic shunt

Wilson's disease

Wilson's disease - serum caeruloplasmin is decreased

Wilson's disease is an autosomal recessive

Definition

- Wilson's disease is an autosomal recessive disorder characterised by impaired copper transport via caeruloplasmin results in excessive copper deposition in the tissues.
- Wilson disease is a disorder resulting from <u>impaired copper excretion into bile</u>. Copper overload and deposition in tissues leads to predominantly hepatic and neuropsychiatric symptoms.
- Metabolic abnormalities include increased copper absorption from the small intestine and decreased hepatic copper excretion.

Aetiology and pathophysiology

- · autosomal recessive
- caused by a defect in the ATP7B gene located on chromosome 13.
- Mutations within the ATP7B gene result in disruption of an ATPase within hepatocytes
 which is responsible for the movement of copper across intracellular membranes. This
 results in hepatic retention of copper, and low serum levels.
- The mechanism of tissue damage in Wilson disease is <u>copper-mediated hydroxyl free</u> radical tissue damage.

Features

- The onset of symptoms is usually between 10 25 years.
- Children usually present with liver disease whereas the first sign of disease in young adults is often neurological disease
- liver: hepatitis, cirrhosis
- neurological:
 - basal ganglia degeneration, speech and behavioural problems are often the first manifestations.
 - > The most common early neurological sign is an asymmetrical tremor,
 - Also: the initial sign is usually increased clumsiness.
 - parkinsonism.
 - dystonia.
 - asterixis,
 - > chorea,
 - dementia
- Kayser-Fleischer rings
 - Golden corneal rings
 - in the posterior surface of the retina, within its Descemet's membrane.
 - Detected by Slit lamp examination
 - Present in up to 90% of symptomatic patients but is not pathognomonic.
- renal tubular acidosis (esp. Fanconi syndrome)
- haemolysis
- blue nails

Diagnosis

- · Reduced serum caeruloplasmin
 - Ceruloplasmin is normal in approximately 5% of cases
- Slit lamp examination

- slit lamp examination will detect Kayser-Fleischer corneal rings in <u>approximately</u> 98% of untreated cases and the sunflower cataract will be more obvious.
- ↓ Total serum copper
- · increased 24hr urinary copper excretion
 - greater than 1.6 µmol/day
- Liver biopsy
 - > The most reliable investigation to confirm the diagnosis
 - Shows:
 - increased hepatic parenchymal copper concentration
 - steatosis, glycogenated nuclei, focal hepatocellular necrosis, fibrosis and cirrhosis.
- MRI of the brain
 - commonly shows increased density in the basal ganglia.
- Genetic testing for ATP7B mutation
 - usually reserved for patients where the diagnosis is in doubt, or for screening of siblings.

Complications

· higher risk of hepatocellular carcinoma.

Management

- · General management
 - Low-copper diet: avoid foods such as organs, shellfish, nuts, and chocolate
 - Hepatotoxic drugs, alcohol and foods high in copper (liver, chocolate, shellfish etc.) should be avoided.
 - Regular check-ups: liver biochemical tests every 6 months if disease is stable^[9]
 - ➤ Liver transplantation in cases of fulminant liver failure
- Medical therapy
 - > Initial therapy: chelating agents
 - Penicillamine:
 - first-line treatment
 - ❖ side effects in ~ 30% of cases
 - ⇒ (e.g., sensitivity reactions)
 - ⇒ bone marrow suppression
 - Alternatives: trientine or zinc salts
 - Trientine
 - ⇒ may become first-line treatment in the future
 - better tolerated than penicillamine, and is therefore used as an alternative where side effects are seen when penicillamine is initiated.
 - > Maintenance therapy: zinc salts or low dose chelating agents
- Zinc acetate is the intervention of choice for patients with asymptomatic Wilson's disease (i.e. those who present with elevated transaminases without evidence of cirrhosis or neurological dysfunction).
- · screening of first degree relatives
 - Once a diagnosis of Wilson's disease is made, screening of first degree relatives (with genetic testing) should be done.

Treatment with a chelating agent should be administered gradually over the course of 3 to 6 months, as mobilizing the copper stored in tissues too rapidly may exacerbate neurological symptoms

Notes & Notes for MRCP

Prognosis

- Early treatment allows a normal length of life,
- however without treatment Wilson's disease is usually fatal by the age of 40 years.

MRCPUK-part-1-September 2014 exam: A 23-year-old woman developed unilateral hand tremor at rest, behaviour & mood changes, speech problems & bradykinesia. Dark circular marks noted around the iris. her uncle died of liver cirrhosis at the age of 40 years. Given the likely diagnosis, what is the mode of inheritance?

→ Autosomal recessive

Hyponatraemia in Patients with chronic liver disease

- Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult.
- Diuretic therapy for the management of ascites often contributes to the hyponatraemia.
- The British Society of Gastroenterology guidelines suggest that:
 - > serum sodium is ≤120 mmol/L→ normal saline + stop diuretic
 - ➤ serum sodium is 126-135 mmol/L → No intervention other than careful monitoring.
 - ➤ serum sodium is 121-125 mmol/L + normal serum creatinine → reduce diuretics or stop it if necessary
 - ➤ serum sodium is 121-125 mmol/L +↑↑ serum creatinine → volume expansion + stop diuretics
 - > fluid restriction should only be used in patients who are clinically euvolaemic, not on diuretics and have severe hyponatraemia with a normal serum creatinine.

Alcohol

After drinking excessive amounts alcohol

- Mechanism of polyuria → Ethanol inhibits ADH secretion
- Mechanism of nausea → vagal stimulation to the vomiting centre.
- Mechanism of tremors → increase glutamate production by neurones to compensate for the previous inhibition by ethanol.
- Mechanism of hypoglycemia → hepatic sequestration of Reduced nicotinamide adenine dinucleotide (NADH)
 - In the liver alcohol dehydrogenase converts ethanol to acetaldehyde but to do so requires the reduction of oxidized nicotinamide adenine dinucleotide (NAD⁺) to reduced nicotinamide adenine dinucleotide (NADH).
 - Acetaldehyde is then further oxidized to acetate to aldehyde dehydrogenase, which requires the reduction of another NAD⁺ to NADH.
 - When excess alcohol is consumed then the system becomes overwhelmed and NADH accumulates in hepatocytes.
 - ➤ This sequestration of NADH reduces the amount of NAD⁺ available to oxidize gluconeogenic precursors → hypoglycemia

Alcohol induced hypoglycemia

- Alcohol metabolized to acetyl-CoA.
- NADH produced during alcohol metabolism interferes with gluconeogenesis.
- NADH causes production of: lactate, malate, and glycerol 3-phosphate.
- Thus, glycerol 3-phosphate causes lipid accumulation in liver alcoholic disease.
- NAD, required for lactate metabolism (and lactate is used for gluconeogenesis), is being used for alcohol metabolism.

The large anion gap and hypoglycemia in alcoholic patients can be explained by which mechanism?

- → Inhibition of dehydrogenase enzymes by NADH
 - Excess alcohol intake leads to accumulation of NADH that <u>decreases</u> gluconeogenesis as well as impairs fatty acid oxidation.
 - (Key <u>gluconeogenic dehydrogenases</u> are inhibited by the elevated levels of NADH, including:
 - lactate dehydrogenase,
 - glycerol 3-phosphate dehydrogenase, and
 - malate dehydrogenase).

Alcohol - drinking problems: management

Nutritional support

 SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- benzodiazepines for acute withdrawal
- disulfram: promotes abstinence alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis
- acamprosate: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo-controlled trials

Disulfiram

- Indication: used as an aid to stop alcohol abuse.
- Mode of action: irreversible inhibitor of aldehyde dehydrogenase, therefore if alcohol is ingested, aldehyde accumulates causing unpleasant reactions including vomiting, palpitations and breathlessness.
- The reaction with alcohol only occurs at least 12 hours after the start of disulfiram therapy and may occur up to 10 days after stopping disulfiram therapy.
- Disulfiram is active against scables, although other treatments are usually preferred.

Alcoholic liver disease

The recommended maximum alcohol intake per week is 21 units for men and 14 units for women. Governmental guidelines suggest that women should not have more than 2-3 units per day and men should not have more than 3-4 units per day

Alcoholic liver disease includes fatty liver, alcoholic hepatitis and cirrhosis.

- fatty liver (hepatic steatosis)
 - accumulation of fat within the hepatocytes.
 - Mechanism:
 - increased generation of NADH reduces the activity of the TCA cycle, the acetyl-Co A is diverted to fatty acid synthesis.
 - reduction in cytosolic NAD⁺ leads to reduced activity of glycerol-3-phosphate dehydrogenase resulting in increased levels of glycerol 3-phosphate which is the backbone for the synthesis of the triglycerides, lead to fatty acid deposition in the liver leading to fatty liver syndrome.
 - asymptomatic and detected incidentally.
 - > Elevated transaminases and a background of alcoholism are clues to the diagnosis.
 - macrovesicular fatty changes.
 - Microvesicular fatty changes are not found in hepatic steatosis.
 - > An ultrasound demonstrates hyper-echogenicity and a bright liver.
 - This is reversible with abstention from alcohol.

- Alcoholic hepatitis presents as:
 - acute right upper quadrant (RUQ) pain
 - Tender hepatosplenomegaly
 - > jaundice
 - > fever
 - frequently occurs on a background of cirrhosis
 - marked derangement of LFTs
 - LFT typically show an AST elevated greater than the ALT with at least a 2:1 ratio
 - AST:ALT ratio can be useful in diagnosing alcoholic liver disease, because more than two-thirds of patients will have a ratio greater than 2.
 - transaminases are typically only slightly elevated rarely over 300 and virtually never over 500.
 - The alkaline phosphatase may well be significantly elevated giving the liver profile an 'obstructive' appearance.
 - High IgA levels are seen in alcoholic liver disease.
 - > At a microscopic level there is inflammation of the liver.
- liver cirrhosis.
 - the hepatocytes are damaged so much that they are replaced by scar tissue which is permanent.
 - Alcoholic hepatitis and cirrhosis may co-exist.
 - Alcoholic hepatitis and cirrhosis may lead to encephalopathy, portal vein hypertension and hepato-renal syndrome, increase risk of infections and they are usually malnourished.
 - There is no specific therapy for alcohol-related hepatitis and cirrhosis.
- Cardiomyopathy of alcoholism is a dilated or congestive form.
- Gout
 - Gout is a common finding in chronic alcoholics.
 - Mechanism:
 - Lactate accumulate in alcoholics causes lactic acidosis (Metabolic acidosis).
 - <u>Lactate competes with uric acid for excretion</u>, decreasing its excretion and thus aggravating gout.

Chronic alcohol abuse is typically associated with → Increased carbohydrate deficient transferrin (CDT)

Which feature would suggest a diagnosis of hepatic steatosis rather than non-alcoholic fatty liver disease?

→ Reversible hepatic damage after discontinuing alcohol consumption

The common abnormalities in chronic alcohol dependence

- Macrocytosis
- Hypertriglyceridaemia can contribute to pancreatitis
- Hyperuricaemia can cause gout
- Hypoglycaemia can contribute to seizures and coma
- Increased carbohydrate deficient transferrin considered a marker of chronic abuse and sometimes checked to ensure abstinence, for example, while awaiting liver transplantation
- Hypogonadism
- Thiamine deficiency
- Abnormal iron
 - ➤ Iron levels are variable in alcohol dependence: hepatitis causes increased serum iron while poor diet can result in iron deficiency
 - > Ferritin can be elevated in the acute phase response, but reduced in advanced liver disease due to possible reduced synthesis rates

- Abnormal electrolytes
 - > Hyponatraemia and hypokalaemia are often seen in established liver disease
 - Hypomagnesaemia
 - hypocalcaemia which may be linked to <u>alcohol-related hypomagnesaemia</u> and poor dietary intake of calcium and vitamin D;
- Elevated liver enzymes
 - Elevated GGT this is due to enzyme induction but does not necessarily indicate that there is liver damage
 - > ALT is elevated in liver disease and hepatocellular damage
 - > AST is elevated (but can also be increased in cardiac or muscular damage).
 - > AST:ALT ratio can be elevated due to the mitochondrial effects of alcohol causing a disproportionate increase in AST. However, this is not specific.

Patients with alcoholic liver disease are often surprisingly <u>sensitive to opiate analgesia</u> which should only be used with caution.

(eg: a patient prescribed dihydrocodeine regularly for abdominal pain associated with chronic pancreatitis, became drowsy with deterioration in his Glasgow coma scale. What is the agent should be administered initially? → Naloxone)

Alcoholic ketoacidosis

Definition

Alcoholic ketoacidosis is a non-diabetic euglycaemic form of ketoacidosis.

Features

- Metabolic acidosis
- Elevated anion gap
- Elevated serum ketone levels
- Normal or low glucose concentration

Treatment

- The most appropriate treatment is an infusion of saline & thiamine.
 - ➤ Thiamine is required to avoid Wernicke encephalopathy or Korsakoff psychosis.

Non-alcoholic fatty liver disease (NAFLD) (Non-alcoholic steatohepatitis (NASH)

Obese T2DM with abnormal LFTs - ? non-alcoholic fatty liver disease

Definition

- liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse.
- NAFLD is subdivided into:
 - ⇒ nonalcoholic fatty liver (NAFL): hepatic steatosis without inflammation
 - ⇒ nonalcoholic steatohepatitis (NASH): hepatic steatosis with hepatic inflammation that may be histologically indistinguishable from alcoholic steatohepatitis
- the diagnosis is made only by histology of liver biopsy which shows lesions suggestive of ethanol intake in a patient known to consume less than 40 g of alcohol per week.

Epidemiology

- Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world.
- relatively common and though to affect around 3-4% of the general population.
- It is projected to become a leading indication for liver transplantation, superseding hepatitis
 C.

Mechanism

 NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome and hence insulin resistance is thought to be the key mechanism leading to steatosis

Associated risk factors

- Obesity
- Hyperlipidaemia
- Type 2 diabetes mellitus
- Jejuno-ileal bypass
- Sudden weight loss/starvation

Complications

- Liver cirrhosis
- NASH is associated with insulin resistance and diabetes.

Features

- Usually asymptomatic
- Hepatomegaly
- Some patients with NASH may complain of fatigue, malaise, and vague right upper abdominal discomfort.

Investigations

- LFT
 - ⇒ ALT is typically greater than AST (ALT > AST = Lipids)
 - ⇒ normal aminotransferase levels do not exclude NAFLD

Radiographic finding:

- ⇒ U/S → increased echogenicity on ultrasound
- ⇒ CT → decreased hepatic attenuation
- \Rightarrow MRI \rightarrow an increased fat signal

Liver biopsy

- ⇒ The hallmark of the condition on liver biopsy is the association of inflammation with fatty infiltration of the liver. This can progress to fibrotic change and eventually to cirrhosis.
- ⇒ fatty infiltration of hepatocytes causing cellular "ballooning" and eventual necrosis.

Diagnosis

- A definitive diagnosis of NAFLD requires all of the following:
 - 1. Demonstration of hepatic steatosis by imaging or biopsy
 - exclusion of common liver disorders like viral hepatitis, alcoholic liver disease, drug induced and autoimmune liver disease (e.g. primary biliary cirrhosis). Exclusion of other causes of hepatic steatosis: e.g:

- Significant alcohol use
- Hepatitis C (particularly genotype 3)
- Wilson disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications
- Reye syndrome
- Acute fatty liver of pregnancy
- HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome
- The confirmatory test for diagnosis is liver biopsy.

Management

- · Non pharmacological: life style management
 - Weight loss: the mainstay of treatment
 - abstinence from alcohol
- Pharmacological
 - there is ongoing research into the role of gastric banding insulin-sensitising drugs (e.g. Metformin)
 - For patients with NASH and diabetes mellitus:
 - Although initial therapy for type 2 diabetes mellitus is typically with metformin, but metformin does not improve liver histology
 - the beneficial impact on liver histology with certain other insulinsensitizing agents could be a consideration when choosing a secondline agent for patients with NASH who cannot take metformin or need additional glucose-lowering therapy. In this setting, pioglitazone and liraglutide are reasonable options.
 - In patients with diabetes mellitus and biopsy-proven NASH, pioglitazone improves fibrosis as well as inflammation and steatosis.
 - use of pioglitazone is limited because it is associated with increased risk of weight gain, heart failure, and fractures.
 - Although less well studied, liraglutide also appears to improve liver biopsy evidence of NASH.
 - Liraglutide is a GLP-1 agonist which results in significant weight loss of up to 7% over 1 year at high dose, (3mg), By driving weight loss it leads to a significant reduction in hepatic fat and may impact on the long-term prognosis of fatty liver disease.

Prognosis

Approximately 20% develop cirrhosis

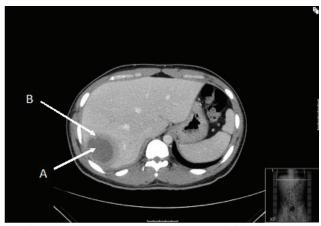
Which liver function test is the best marker of non-alcoholic fatty liver disease in type 2 diabetes mellitus?

→ alanine aminotransferase

Liver abscess

Pyogenic liver abscess

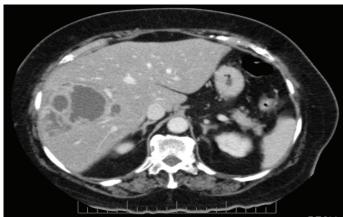
- The most common organisms found in pyogenic liver abscesses are *Staphylococcus* aureus in children and *Escherichia coli* in adults.
- usually complicates pre-existing biliary and gastrointestinal tract infections.
- Management
 - Ideally, a penicillin-based β-lactamase antibiotic combined with metronidazole to provide anaerobic cover would be the treatment of choice.
 - > amoxicillin + ciprofloxacin + metronidazole
 - > if penicillin allergic: ciprofloxacin + clindamycin



The CT demonstrates a hypodense lesion (A) with surrounding oedema (B).

Amoebic liver abscess

- A solitary abscess in the right lobe of the liver is typical of amoebic liver abscess.
 - > The collection is commonly single and confined to the right lobe, but multiple leftsided abscesses may also occur.
- Liver abscesses due to amoebae mainly occur in endemic tropical countries.
- A history of chronic diarrhoea might be elicited in patients with amoebic liver abscess.
- Clinical presentation can be indistinguishable from pyogenic abscesses.
- Specific anti-E. histolytica antibodies can be found in 90%
- Management
 - > 10-day course of metronidazole.
 - For larger liver abscesses aspiration is the intervention of choice, combined with antibiotic therapy.



CT showing a pyogenic liver abscess in the right lobe of the liver.

Hydatid cysts

Asymptomatic, calcified cystic lesions in the liver are typical of hydatid cysts.

- Hydatid cysts are endemic in Mediterranean and Middle Eastern countries.
- Hydatid infection was endemic in sheep farming regions (such as Wales or New Zealand) in the past and sheep dogs were infected by eating infected offal. Humans contract hydatids via faecal/oral spread from dogs.
 - > most commonly seen in farming and rural communities
- They are caused by the tapeworm parasite Echinococcus granulosus.
- Up to 90% cysts occur in the liver and lungs
- An outer fibrous capsule is formed containing multiple small daughter cysts.
- These cysts are allergens which precipitate a type 1 hypersensitivity reaction.

Clinical features:

- Can be asymtomatic, or symptomatic if cysts > 5cm in diameter
 - The liver cysts are usually asymptomatic, and calcification usually denotes a non-viable cyst.
- Morbidity caused by cyst bursting, infection and organ dysfunction (biliary, bronchial, renal and cerebrospinal fluid outflow obstruction)
- In biliary rupture there may be the classical triad of; biliary colic, jaundice, and urticaria

Investigations

- Ultrasonography is the most helpful **initial test** since it can usually differentiate a simple cyst from other cystic lesions. It should also be used for follow up studies.
- CT scan shows characteristic daughter cysts.
- · Hydatid serology has a sensitivity of 80-90%.
- If hydatid serology is negative, then further imaging (CT/MRI) +/- aspiration may be required to make a diagnosis.
- CT is the best investigation to differentiate hydatid cysts from amoebic and pyogenic cysts.

Treatment

- Surgery is the mainstay of treatment (the cyst walls must not be ruptured during removal and the contents sterilised first).
- benzimidazoles

Drug-induced liver disease

Flucloxacillin + co-amoxiclav are well recognised causes of cholestasis

Notes

- with co-amoxiclav, a four-week delay in symptoms and signs is not unusual.
- ** with erythromycin risk may be reduced with erythromycin stearate

Epidemiology

commoner in women

Features

- jaundice (elevated bilirubin)
- · hepatomegaly,
- deranged transaminases
- · associated with anti-LKM2 autoantibodies.

Differential diagnosis

- autoimmune hepatitis
 - may also be associated with anti-LKM positivity,
 - short history and drug exposure make drug-induced hepatitis more likely.

Prognosis

Liver function can improve after drug withdrawal, but relapses are possible.

Budd-Chiari syndrome

Triad of abdominal pain, ascites and liver enlargement.

Definition

- obstruction of the main hepatic veins by thrombus.
- Budd-Chiari syndrome, or hepatic vein thrombosis, is usually seen in the context of underlying haematological disease or another procoagulant condition

Causes

· polycythaemia rubra vera

- thrombophilia: activated protein C resistance, antithrombin III deficiency, protein C & S deficiencies
- pregnancy
- · oral contraceptive pill

Features

- · abdominal pain: sudden onset, severe
- ascites
- tender hepatomegaly
- Signs of portal hypertension are present and patients may develop acute variceal haemorrhage as a complication.

Diagnosis

- Ultrasound Doppler or contrast CT scan is often used to make the diagnosis.
 - Hypertrophy of the caudate lobe on imaging is a characteristic sign but is seen in only 50% of cases.
- Ascitic tap usually demonstrates a high SAAG (>11 g/L).

Management

· Thrombolysis and subsequent anticoagulation

Prognosis

 Three-year survival in patients with chronic Budd-Chiari syndrome has been reported as 50%.

Gilbert's syndrome

- Gilbert's syndrome is an <u>autosomal recessive</u> condition of defective bilirubin conjugation due to a <u>deficiency of UDP glucuronyl transferase</u>.
- The prevalence is approximately 1-2% in the general population

Features

- unconjugated hyperbilinaemia (i.e. not in urine)
- normal dipstix urinalysis excludes Dubin-Johnson and Rotor syndrome as these both produce a conjugated bilirubinaemia.
- jaundice may only be seen during an intercurrent illness

Investigation

rise in bilirubin following prolonged fasting or IV nicotinic acid

Management

no treatment required

Crigler-Najjar syndrome

- Crigler-Najjar syndrome refers to a condition of absent UDP-glucuronyl transferase.
- This condition presents early in life with jaundice, increased unconjugated bilirubin and kernicterus.
- This disease is life threatening and the only cure is liver transplant.

Dubin-Johnson syndrome

- benign autosomal recessive disorder
- Resulting in hyperbilirubinaemia (conjugated, therefore present in urine).
- It is due to a defect in the canillicular multispecific organic anion transporter (cMOAT) protein. This causes defective hepatic bilirubin excretion
- patients have a black liver on gross examination of the tissue.
- On microscopic examination, patients have epinephrine metabolite accumulations in their hepatocytes.
- No treatment is necessary.

Autoimmune hepatitis

The combination of **deranged LFTs** combined with **secondary amenorrhoea** in a **young female** strongly suggest \rightarrow **autoimmune hepatitis**

- Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in young females.
- · more common in females.

Pathophysiology

• T-cell mediated progressive necro-inflammatory process resulting in fibrosis and cirrhosis.

Associations

- Other autoimmune disorders including:
 - coeliac disease.
 - > pernicious anaemia.
 - > thyroiditis
 - > type 1 diabetes mellitus.
- IgG hypergammaglobulinaemia
- sicca syndrome (xerostomia/dry eyes, keratoconjunctivitis sicca) may occur.
- HLA B8, DR3 and Dw3.

Disease	Associated raised immunoglobulin subtype
Alcoholic liver disease	IgA
Primary biliary cirrhosis	IgM
Autoimmune hepatitis	IgG

Types

• Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present

Type I	Type II	Type III
Anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA). Affects both adults and children	Anti-liver/kidney microsomal type 1 antibodies (LKM1) Affects children only	Soluble liver-kidney antigen Affects adults in middle-age

Features

- may present with signs of chronic liver disease
- acute hepatitis: fever, jaundice etc (only 25% present in this way)
- amenorrhoea (common)

Investigations

- ANA/SMA/LKM1 antibodies,
- raised IgG levels
- liver biopsy:
 - The gold standard for diagnosis
 - inflammation extending beyond limiting plate 'piecemeal necrosis', bridging necrosis

Management

- steroids, other immunosuppressants e.g. azathioprine
 - > Prednisolone (with or without azathioprine) is better than azathioprine alone.

- Steroid therapy produce symptomatic, biochemical and histological improvement, with improvement in survival.
- It does not, however, prevent progression to frank cirrhosis.
- liver transplantation

Prognosis

 The prognosis with long-term immunosuppression is excellent even in the presence of cirrhosis and few patients subsequently develop liver failure.

Ischaemic hepatitis

- Ischaemic hepatitis is a diffuse hepatic injury resulting from acute hypoperfusion (sometimes known as 'shock liver').
- It is diagnosed in the presence of an inciting event (eg: cardiac arrest) and marked increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal).
- Often, it will occur in conjunction with acute kidney injury (tubular necrosis) or other end organ dysfunction.

Pregnancy: jaundice

Physiological liver changes during pregnancy

- albumin level decreases earlier in 1st trimester due to hemodilution
- ALT& AST aminotransferase remains normal. Thus, serum aminotransferase levels is the most useful test for the routine diagnosis of liver diseases during pregnancy.
- total and free bilirubin decreases during all three trimesters. Conjugated bilirubin ↓↓in 2nd & 3rd trimesters.
- Serum gamma-glutamyl transferase ↓↓ in 2nd & 3rd trimesters,
- serum 5'nucleotidase slightly ↑↑ in 2nd & 3rd trimesters.
- Serum total bile acid concentrations not changed during pregnancy. Measurement of serum bile acids may be useful for the diagnosis of cholestasis, especially when serum aminotransferase levels are within normal limits.
- Intrahepatic cholestasis of pregnancy would not occur in the first trimester.

Gilbert's & Dubin-Johnson syndrome,

may be exacerbated during pregnancy

HELLP syndrome

- HELLP syndrome is a mnemonic that stands for Hemolysis, Elevated Liver enzymes, and Low Platelets in a patient with severe preeclampsia.
- HELLP syndrome is a manifestation of severe preeclampsia that can lead to hepatic subcapsular hematoma formation.
- Schistocytes are an erythrocyte variant that may be seen in HELLP syndrome.
- Immediate delivery is the only definitive treatment

Obstetric cholestasis

Epidemiology

- Obstetric cholestasis affects around 0.7% of pregnancies in the UK
- most common in the third trimester

Pathophysiology

· Caused by a bile acid transporter defect

Features

- pruritus may be intense typical worse palms, soles and abdomen
- Jaundice occurs in less than 10% of patients.

Diagnosis (cholestatic picture of (LFTs) with a high ALP and, with a lesser rise in ALT.)

- ↑ Total Serum bile acid levels (cholic acid and chenodeoxycholic acid) >10 micromol/L
- ↑↑ GGT
- ↑ ALT, AST
- ↑ direct bilirubin
 - ➤ bilirubin < 100
 - > only slightly elevated in about 10%
- ↑ ALP
 - > ALP is not useful as it is normally raised in late pregnancy anyway.
- prothrombin time may be prolonged in any cholestatic process due to vit k deficiency

Complications

• increased risk of prematurity and still birth.

Differential diagnosis:

 Viral hepatitis is the commonest cause of jaundice in pregnancy but the elevated bile acids make this unlikely

Management

- ursodeoxycholic acid
 - First-line medication
 - widely used but evidence base not clear
 - early therapy with ursodeoxycholic acid reduces the risk of preterm birth and stillbirth.
- Cholestyramine
 - SE: may cause a deficiency in fat-soluble vitamins
 - Rarely, there are cases of cerebral hemorrhage associated with vitamin K shortage under cholestyramine therapy.
- induction of labour at 37 weeks is common practice but may not be evidence based
- vitamin K supplementation
- phenobarbital

Prognosis

- fully reversible postpartum
- Recurrence in following pregnancies (40–60%)

Cardiac output and blood volume increase in pregnancy but hepatic blood flow does not.

Acute fatty liver of pregnancy (AFLP)

Definition

 a rare disease most common in the third trimester characterized by extensive fatty infiltration of the liver, which can result in acute liver failure

Risk factors

- older maternal age.
- primiparity,

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- multiple pregnancies,
- pre-eclampsia,
- · male foetus
- previous AFLP.

Pathophysiology

• dysfunction of fatty acid β -oxidation \rightarrow microvesicular fat deposition.

Features

- abdominal pain
- nausea & vomiting
- headache
- jaundice
- hypoglycaemia
- severe disease may result in pre-eclampsia
- Coagulopathy with an increased risk of disseminated intravascular coagulation (DIC)
- Hypoalbuminemia → ascites
- encephalopathy later.

Investigations

- ALT is typically elevated e.g. 500 u/l
- ↑ WBC, ↓ platelets

Management

- · support care
- · once stabilised delivery is the definitive management

Haemochromatosis

Haemochromatosis is autosomal recessive

 Haemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation.

Aetiology

- It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*.
 - *there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene
- 90 % of cases are caused by the substitution of tyrosine for cysteine at position 282 of the HFE gene found on chromosome 6.
- HLA-A3 is associated with haemochromatosis

Epidemiology

- 1 in 10 people of European descent carry a mutation genes affecting iron metabolism, mainly HFE
- prevalence in people of European descent = 1 in 200
- Haemochromatosis is the most prevalent genetic condition in Caucasian population, with a carrier rate of 1 in 10 and is present in about 1 in 200-400 people
- Males and females are affected equally but females are often 'protected' from the clinical features by menstrual blood loss.

Pathophysiology

- Iron absorption is regulated in the duodenal crypts.
- HFE is a protein that regulates iron absorption.
- HFE → forms a complex at the basolateral membrane that if bound to transferrin + iron at
 the basolateral membrane of the duodenal crypt cells prevents maturation and
 consequently absorption of iron in the bowel.
- mutation in the HFE gene → failure of complex formation and constant maturation of duodenal crypt cells → subsequent unregulated uptake of iron.

Presenting features

- often asymptomatic in early disease
- · early symptoms include
 - fatigue,
 - > erectile dysfunction
 - arthralgia (often of the hands)
 - Joint x-rays characteristically show chondrocalcinosis
- 'bronze' skin pigmentation
- · diabetes mellitus
- liver: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition)
- cardiac failure (2nd to dilated cardiomyopathy)
- hypogonadism (2nd to cirrhosis and pituitary dysfunction hypogonadotrophic hypogonadism)
- arthritis (especially of the hands). Joint x-rays characteristically show chondrocalcinosis

Questions have previously been asked regarding which features are reversible with treatment:

Reversible complications

- Cardiomyopathy
- Skin pigmentation

Irreversible complications

- Liver cirrhosis**
- Diabetes mellitus
- · Hypogonadotrophic hypogonadism
- Arthropathy

**whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not Investigation

Screening for haemochromatosis

- general population: transferrin saturation > ferritin
- · family members: HFE genetic testing

The best investigation to screen for haemochromatosis

- General population: transferrin saturation is considered the most useful marker.
 - Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation.
- testing family members: genetic testing for HFE mutation

These guidelines may change as HFE gene analysis become less expensive **Diagnostic tests**

- liver biopsy: Perl's stain
 - the gold standard investigation (as it quantifies iron deposition and also stages the amount of fibrosis)
- molecular genetic testing for the C282Y and H63D mutations
 - ➤ found in 90%
 - there is substitution of tyrosine for cysteine at position 282 of the HFE gene on chromosome 6.
 - However, there is low penetrance of clinical disease and haemochromatosis also occurs in patients who are negative for this mutation.
 - genetic testing for HFE gene mutations is indicated for an individuals meeting one of the following criteria:
 - Elevated serum ferritin (> 300 microgram / L in males; > 200 microgram / L in females)
 - Elevated transferrin saturation (> 45 %)
 - First degree relative with haemochromatosis
- MRI has high specificity but low sensitivity for demonstrating iron overload in the liver it
 has not replaced the need for biopsy in the majority of cases.

Typical iron study profile in patient with haemochromatosis

- transferrin saturation > 55% in men or > 50% in women
- raised ferritin (e.g. > 500 ug/l).
 - Ferritin is measured to help guide further investigation and treatment:
 - if more than 1000 a liver biopsy should be performed, and treatment initiated.
- low TIBC

Diabetes and impotence associated with high ferritin \rightarrow haemochromatosis

- The combination of DM and hypogonadotrophic hypogonadism (HH) (low testosterone & FSH)) is compatible with a diagnosis of haemochromatosis and measuring ferritin would be a reasonable investigation.
- The next investigation would be measurement of transferrin saturation

Treatment

- Venesections
 - survival and morbidity are improved if phlebotomy is initiated prior to the development of cirrhosis.
 - > weekly or twice weekly (if tolerated) venesections of 500 cm³ until the serum ferritin is less than 50 ng/mL & transferrin saturation less than 50%
- Chelation with desferrioxamine
 - > When iron overload and anaemia are present concomitantly.
 - may be utilised where venesection cannot be continued and there is still evidence of iron overload.
 - > It is more commonly used in other conditions associated with iron overload such as thalassaemia major.
- Avoid vitamin C supplementation
 - > as this can enhance iron toxicity.
- liver transplantation
 - > End stage liver disease, portal hypertension and hepatocellular carcinoma (which is increased up to 200-fold) may necessitate liver transplantation.

Monitoring adequacy of venesection

 BSCH recommend 'transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l'

MRCPUK-part-1-May 2005 exam: Which feature of haemochromatosis may be reversible with treatment?

→ Cardiomyopathy

MRCPUK-part-1-May 2014 exam: H/O fatigue and arthralgia. The joint pain is worse around his metacarpophalangeal joints and knees. polyuria and polydipsia. An x-ray of his knees reveals chondrocalcinosis. What is the mode of inheritance of the likely underlying diagnosis?

- → Autosomal recessive
 - (This patient has typical symptoms of haemochromatosis: 1/ Lethargy.
 2/arthralgia, with evidence of chrondrocalcinosis. 3/diabetes mellitus (polyuria and polydipsia)

MRCPUK-part-2-march-2018: abnormal liver function, low testosterone level, diabetes mellitus and elevated serum ferritin level. What is the most effective intervention to treat

iron overload?

→ Venesection

\(\Delta\) haemochromatosis.

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma

- · hepatitis B most common cause worldwide
- hepatitis C most common cause in Europe
- Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide.
- Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being the most common cause in Europe.

Risk factors

- The main risk factor for developing HCC is
 - Liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis.
 - *Wilson's disease is an exception
 - 75% to 90% of patients with HCC have cirrhosis.
 - HCC develops in 4% of cirrhotics per year.
 - Patients with chronic hepatitis B have 100-fold higher risk of developing HCC.
- Other risk factors include:
 - alpha-1 antitrypsin deficiency
 - hereditary tyrosinosis
 - > glycogen storage disease
 - aflatoxin
 - > drugs: oral contraceptive pill, anabolic steroids
 - porphyria cutanea tarda
 - male sex
 - > diabetes mellitus, metabolic syndrome

Features

- · tends to present late
- features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- possible presentation is decompensation in a patient with chronic liver disease

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:

- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol

Management options

- · early disease: surgical resection
- liver transplantationradiofrequency ablation
- transarterial chemoembolisation
- sorafenib: a multikinase inhibitor

Management of liver capsule pain

- Stretching of the liver capsule by a primary hepatoma or metastases within the liver can cause chronic cancer pain.
- This commonly presents as dull, right-sided subcostal pain.
- Referred pain at the top of the ipsilateral shoulder occurs due to diaphragmatic irritation if the superior aspect of the capsule is involved.

- Corticosteroids can be used in the management of liver capsule pain and dexamethasone is usually the choice of steroid.
- Which analgesics would be most suitable for the management of liver capsule pain?
 Dexamethasone

Carcinoid syndrome

Flushing, diarrhoea, bronchospasm, tricuspid stenosis, pellagra \rightarrow carcinoid with liver mets - diagnosis: urinary 5-HIAA

Which biochemical markers is most likely depleted in carcinoid syndrome?

- → Biosynthesis of serotonin begins with tryptophan, so tryptophan depletion is most likely.
- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver

Features

- flushing (often earliest symptom)
- diarrhoea
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
 - (mostly tricuspid insufficiency) and pulmonary stenosis,
 - Endocardial fibrosis is due to constant exposure of the right heart to serotonin.
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour Investigation
 - urinary 5-hydroxy-indole-acetic acid (5-HIAA) (specificity 100%, sensitivity 70%)
 - plasma chromogranin A y (The most sensitive marker 100%)

Management

- somatostatin analogues e.g. Octreotide (Side effects of octreotide therapy include increased risk of gallstones)
 - > The best treatment for symptoms of carcinoid is the somatostatin analogue, octreotide, which improves symptoms and prognosis
- Other potential treatments following resistance or failure of octreotide include hepatic artery embolisation.
- diarrhoea: cyproheptadine may help
 - ➤ the treatment for the diarrhoea will be through treating the underlying diagnosis, which is carcinoid → octreotide
 - Cyproheptadine is not a first line treatment for diarrhoea and in fact may cause diarrhoea as a side effect.
 - ➤ Telotristat →inhibits tryptophan hydroxylase, which mediates serotonin biosynthesis. It is indicated for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.
 - Telostristat approved by (FDA) in 2017 for carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by an SSA.

Which vitamin deficiency may be associated with carcinoid syndrome?

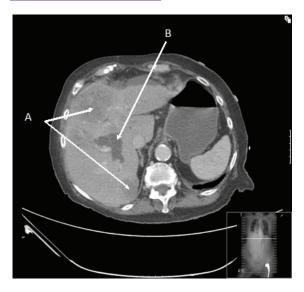
→ Vitamin B₃

- Vitamin B₃, niacin, is used to make NAD and is derived from tryptophan.
- In carcinoid syndrome, the increased synthesis of serotonin would deplete the supply of tryptophan needed to make niacin.
- A deficiency of niacin would result in pellagra, which is characterized by diarrhea, dermatitis, and dementia

MRCPUK-part-1-May 2007 exam: If the patient develops carcinoid syndrome, which one of the following symptoms is most likely to occur first?

→ Facial flushing

hepatic metastases



The abdominal CT demonstrates a number of ill-defined low-density deposits in the liver consistent with hepatic metastases (A) along with significant intrahepatic biliary duct dilatation (B). The likely diagnosis is metastatic pancreatic cancer causing biliary obstruction with a concomitant cholangitis.

Viral hepatitis

Hepatitis A (HAV)

The classic story of (HAV) is initial GIT symptoms then improved condition followed by jaundice and very high alanine aminotransferase (ALT) .

Diagnosis

- Anti-hepatitis A IgM antibody will confirm the diagnosis
- IgG antibody would suggest:
 - a previous hepatitis A infection or
 - > another underlying cause such as cytomegalovirus.

Indicator of poor prognosis

 Hepatitis A infection on a background of hepatitis C (but not B) has very poor prognosis.

Hepatitis B

Deterioration in patient with hepatitis B - ? hepatocellular carcinoma

• Hepatitis B is a double-stranded DNA hepadnavirus

Spread through

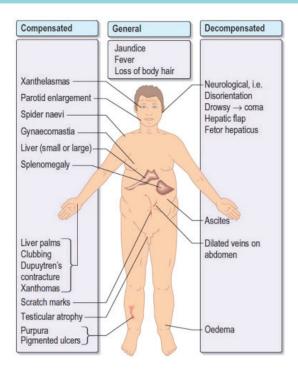
- · vertical transmission from mother to child.
 - > Perinatal transmission is the most common route of hepatitis B infection
 - ➤ the infection rate is 90% in infants born to HBeAg (hepatitis B envelope antigen) positive mothers.
- exposure to infected blood or body fluids,
 - Sexual transmission comprises 30% of hepatitis B infections in developed countries.

Incubation period

6-20 weeks.

Features:

- · fever.
- jaundice
- elevated liver transaminases.
 - > (ALT) will be elevated more than (AST).
- Symptoms of decompensated liver disease include:
 - ascites.
 - > encephalopathy and
 - gastrointestinal haemorrhage.



Complications

- chronic hepatitis (5-10%)
- fulminant liver failure (1%)
- hepatocellular carcinoma
- polyarteritis nodosa
 - the vascular extrahepatic manifestation of hepatitis B.
 - ➤ There is a hepatitis <u>B</u> seropositivity in 30% of patients with polyarteritis nodosa.
- cryoglobulinaemia
- hematologic extrahepatic manifestation of hepatitis B → Aplastic anemia
- renal extrahepatic manifestations of hepatitis B
 - Membranous glomerulonephritis (more common)
 - > membranoproliferative glomerulonephritis (less common) are.

Prognosis

Most adults with hepatitis B will progress to full resolution.

Immunisation against hepatitis B

- · contains what?:
 - HBsAg adsorbed onto aluminium hydroxide adjuvant
- prepared from what?
 - > prepared from yeast cells using recombinant DNA technology
- schedule?
 - give 3 doses of the vaccine + one-off booster 5 years following the initial primary vaccination
- At risk groups who should be vaccinated include:
 - healthcare workers.
 - intravenous drug users,
 - sex workers,

- > close family contacts of an individual with hepatitis B.
- individuals receiving blood transfusions regularly,
- > chronic kidney disease patients who may soon require renal replacement therapy,
- prisoners.
- chronic liver disease patients
- failure to respond or respond poorly to 3 doses of the vaccine
 - occur in 10-15% of adults.
 - Risk factors include:
 - age over 40 years,
 - obesity,
 - smoking,
 - alcohol excess and
 - immunosuppression
 - how to check response?
 - testing for anti-HBs levels
 - testing for anti-HBs is only recommended for:
 - those at risk of occupational exposure (i.e. Healthcare workers) and
 - patients with chronic kidney disease.
 - In these patients anti-HBs should be checked 1-4 months after primary immunisation
 - how to interpret anti-HBs levels? the table below shows

Anti-HBs level (mIU/ml)	Response
> 100	Indicates adequate response , no further testing required. Should still receive booster at 5 years
10 - 100	Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required
< 10	Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus

Hepatitis B serology

HBsAg = ongoing infection, either acute or chronic if present > 6 months anti-HBc = caught, i.e. negative if immunized

Interpreting hepatitis B serology: It is important to remember a few key facts:

- surface antigen (HBsAg)
 - > is the first marker to appear and causes the production of anti-HBs
 - appears in the serum 1 to 10 weeks following acute exposure, even before symptoms or (ALT) rise.
 - normally implies acute disease (present for 1-6 months)
 - if present for > 6 months then this implies chronic disease (i.e. Infective)
 - In those who recover HBsAg will usually become undetectable after 4 to 6 months.
- Anti-HBs

- implies immunity (either exposure or immunisation).
- > It is negative in chronic disease

Anti-HBc

- implies previous (or current) infection.
 - IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months.
 - ❖ Anti-HBc IgM is detectable between 6 and 32 weeks after exposure
 - IgG anti-HBc persists

HbeAg

- results from breakdown of core antigen from infected liver cells as is therefore a marker of infectivity
- HBeAg is a marker of infectivity in all patients except those who have Hepatitis B virus (HBV) pre-core mutant or the core promoter mutant, because they do not synthesise HbeAg,
 - this is most commonly due to a stop-codon mutation at nucleotide 1896.
- So the learning here is that although the e antigen is negative, the patient may still be infective.
- previous immunisation: anti-HBs positive, all others negative
- previous hepatitis B (> 6 months ago), not a carrier: anti-HBc positive, HBsAg negative
- previous hepatitis B, now a carrier: anti-HBc positive, HBsAg positive

IgM anti-HBc jointing HBV-DNA is most effective and most practicable in distinguishing Acute Hepatitis B from Chronic Hepatitis B With Acute Flare.

	Acute Infection	Chronic Carrier	Window Period	Complete Recovery	Immunized
HBs	+	+	-	-	-
Anti-HBs	-	-	-	+	+
Anti-HBc	+ (IgM)	+ (IgG)	+	+ (lgG)	-

HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronically infected
HBsAg anti-HBc anti-HBs	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

HBeAg-positive chronic hepatitis B and compensated liver disease		
1st line	Peginterferon alfa-2a (48-week course)	
2nd line (if HBV DNA level has decreased by less than 2 log10 IU/ml and/or if HBsAg is > 20,000 IU/ml after 24 weeks from starting 1st line)	Tenofovir. Or alternatively (if tenofovir not tolerable) Entecavir	
3rd line (if HBV DNA remains detectable at 96 weeks)	If no history of lamivudine resistance: add lamivudine to tenofovir.	
	If there is history of lamivudine resistance: add entecavir to tenofovir	

HBeAg-negative chronic hepatitis B and compensated liver disease		
1st line	Peginterferon alfa-2a (48-week course)	
2nd line (if HBV DNA level has decreased by less than 2 log ₁₀ IU/ml and HBsAg has not decreased after 24 weeks from starting 1st line)	entecavir <mark>or</mark> tenofovir	
3rd line (if HBV DNA remains detectable at 48 weeks)	switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil	

Distinguish between acute HBV and a flare of chronic disease

- originates from an area of the world with a high prevalence of HBV infection
 - In areas of low HBV prevalence, such as the United Kingdom, a combination of HBsAg positivity and features of acute hepatitis usually indicates acute self-limiting hepatitis B infection.
 - > In countries with high prevalence of hepatitis B the majority of infection is acquired vertically during childhood and leads to chronicity rather than acute infection.

- Anti-HBc-IgM is typically found in acute HBV infection; however it can be found in10-15% of patients with chronic HBV. This is especially true when considering acute flares of chronic hepatitis.
 - ➤ The sensitivity and specificity for HBc-IgM to distinguish between acute HBV and a chronic flare has been reported as low as 77% and 70% respectively.
 - Using high titres to determine cut-offs (1:10,000 or greater) does improve this significantly however.
- Flares of chronic HBV are typically associated with higher levels of HBV DNA and AFP than acute self-limiting disease.
 - The alpha-fetoprotein is commonly elevated during acute hepatitis <u>due to hepatic</u> regeneration.
- flares of chronic HBV tend to be associated with less necroinflammation, and thus ALT tends to be as raised as in acute HBV, but hepatic synthetic dysfunction is more common

Distinguish between patients who have recovered from hepatitis B and those immunized for it

Although both patients who have recovered from hepatitis B and those immunized for it will
test positive for antibody to hepatitis B surface antigen, only patients who have recovered
from hepatitis B will be positive for IgG antibody to hepatitis B core antigen.

Assessment of liver disease in secondary specialist care for adults with chronic hepatitis B

- The initial test for liver disease in adults newly referred for assessment is → transient elastography
 - Transient elastography (FibroScan) is a new, non-invasive, rapid method allowing evaluation of liver fibrosis by measurement of liver stiffness.
 - Interpretation of transient elastography score
 - ≥ 11 kPa → antiviral treatment without a liver biopsy
 - between 6 and 10 kPa → liver biopsy to confirm the level of fibrosis
 - < 6 kPa → liver biopsy, if the:</p>
 - Age < 30 years and HBV DNA > 2000 IU/ml and abnormal ALT (≥30 IU/L for males and ≥ 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.
 - - ❖ HBV DNA < 2000 IU/ml and normal ALT.</p>
 - Offer annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Interpretation of transient elastography score in chronic HBV			
(NICE guide	(NICE guidelines 2017) (PassOnExam		
≥ 11 kPa 6 – 10 kPa ≤ 6 kPa			
Offer antiviral treatment without a liver biopsy	Consider liver biopsy to confirm the level of fibrosis	Offer liver biopsy only if: 1) younger than 30 years and 2) have HBV DNA greater than 2000 IU/ml and 3) abnormal ALT (≥ 30 IU/L for males and ≥ 19 IU/L for females) on 2 consecutive tests conducted 3 months apart	

Management

- Acute HBV
 - the majority of patients will resolve spontaneously,
 - treatment with an oral anti-HBV agent is not necessary.

Patients who are positive for HBsAg for more than six months but are HBeAg negative, HBV DNA negative and have normal ALT do not require liver biopsy nor do they require antiviral therapy, but hepatitis B serology and ALT should be monitored annually.

- Chronic HBV
 - Indications of antiviral treatment in adults with chronic hepatitis B (NICE 2013)
 - age ≥ 30 years + HBV DNA > 2000 IU/ml + abnormal ALT (≥30 IU/L in males
 ≥19 IU/L in females) on 2 consecutive tests conducted 3 months apart.
 - Age < 30 years + HBV DNA > 2000 IU/ml + abnormal ALT if there is:
 - evidence of necro-inflammation or fibrosis on liver biopsy
 - or a transient elastography score > 6 kPa.
 - HBV DNA > 20,000 IU/ml + abnormal ALT regardless of age or the extent of liver disease. (on 2 consecutive tests conducted 3 months apart)
 - cirrhosis + detectable HBV DNA, regardless of HBeAg status, HBV DNA and ALT levels.
 - HBV DNA > 2000 IU/ml + evidence of necro-inflammation or fibrosis on liver biopsy.
 - > with compensated liver disease
 - First-line → 48-week course of pegylated interferon-alpha
 - ❖ → ↓ ↓ viral replication in up to 30% of chronic carriers.
 - better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy</p>
 - Interferon alfa is usually given short term and is not very effective in patients without an elevated ALT.
 - stopping peginterferon alfa-2a 24 weeks after starting treatment if HBV DNA level has decreased by less than 2 log₁₀ IU/ml and/or if HBsAg is greater than 20,000 IU/ml → 2nd line
 - second-line → tenofovir disoproxil (nucleotide analogue, reverse transcriptase inhibitor (NRTI)

- to people who do not undergo HBeAg seroconversion or who relapse (revert to being HBeAg positive following seroconversion) after firstline treatment with peginterferon alfa-2a.
- would be of most value for long-term treatment of HBV
- Offer entecavir (nucleoside analogue, reverse transcriptase inhibitor) as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.
- ⇒ Entecavir is a pro-drug and requires phosphorylation to the triphosphate form before it becomes active.

```
Nucleoside = Sugar + Base
Nucleotide = Sugar + Base + Phosphate
```

- Lamivudine would be an alternative, although resistance develops commonly.
- If HBV DNA remains detectable at 96 weeks:
 - ❖ If No history of lamivudine resistance → add lamivudine to tenofovir disoproxil.
 - ❖ With a history of lamivudine resistance → add entecavir to tenofovir disoproxil.
- with decompensated liver disease (portal hypertension, bleeding varices, ascites and encephalopathy)
 - Do not offer peginterferon alfa-2a → worsen hepatic decompensation
 - First-line → entecavir (if there is no history of lamivudine resistance).
 - people with a history of lamivudine resistance → tenofovir disoproxil
- When to consider stopping nucleoside or nucleotide analogue treatment?
 - without cirrhosis → 12 months after HBeAg seroconversion
 - with cirrhosis → do not stop
- Co-infection with chronic hepatitis B and C → peginterferon alfa + ribavirin

In	Indications of starting antiviral			
tre	treatment in chronic HBV			
(NI	CE guidelines 2017) (PassOnExam)			
1	HBV DNA > 2000 IU/ml + abnormal ALT			
	+ age > 30 years			
2	HBV DNA > 2000 IU/ml + abnormal ALT			
	+ age < 30 years + necroinflammation			
	or fibrosis on liver biopsy or a transient			
	elastography score > 6 kPa.			
3	HBV DNA > 20,000 IU/ml + abnormal			
	ALT			
4	cirrhosis + detectable HBV DNA			
5	HBV DNA > 2000 IU/ml +			
	necroinflammation or fibrosis on liver			
	biopsy.			

Chronic HBV with decompensated		
liver disease (NICE guidelines 2017)		
Without a history of entecavir		
lamivudine resistance		
with a history of	tenofovir	
lamivudine resistance. disoproxil		
Do not offer peginterferon alfa-2a to people with		
chronic HBV and decompensated liver disease.		

Hepatitis B and pregnancy

Risk of vertical transmission

- Without intervention the vertical transmission rate is around 20%,
- increases to 90% if the woman is positive for HBeAg.
- there is little evidence to suggest caesarean section reduces vertical transmission rates

Treatment

- Treatment of the baby:
 - babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a complete course of vaccination + hepatitis B immunoglobulin
 - Breastfeeding
 - hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)
 - they may continue antiviral treatment while they are breastfeeding.
- Treatment of the woman:
 - > all pregnant women are offered screening for hepatitis B
 - Interferon is contraindicated
 - Offer tenofovir disoproxil to women with HBV DNA > 10⁷ IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby.
 - Monitor quantitative HBV DNA <u>2 months after starting tenofovir</u> disoproxil and <u>ALT</u> monthly after the birth to detect postnatal HBV flares in the woman.
 - Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment

Hepatitis C

Hepatitis C - 80-85% become chronically infected

- Hepatitis C is likely to become a significant public health problem in the UK in the next decade.
- It is thought around 200,000 people are chronically infected with the virus.
- The most common route of transmission of hepatitis C in the United States is intravenous drug use.
- Zone I of the liver is the zone first affected by hepatitis C infection.
- Hepatitis C virus genotypes
 - There are 6 genotypes and more than 50 subtypes.
 - In England and Wales genotypes 1 and 3 account for more than 90% of all diagnosed infections.
 - In Japan, North America, and western Europe, the majority of infections are with genotypes 1, 2, and 3.
 - Subtype 1a is the most predominant genotype in the US,
 - subtype 1b predominates in Asia and Europe.

- Genotype 4 is more prevalent in the middle east and in northern and central Africa.
- Genotypes 5 and 6 have been identified in South Africa and southeast Asia, respectively.
- Differences in subtype can result in subtle differences in response to antiviral therapies.
- Hepatitis C genotype 3 is associated with insulin resistance and hepatic steatosis
- > Genotype 3a is most strongly associated with a positive response to therapy
- Genotypes 2 and 3 respond reasonably well to polyethylene glycol (PEG) interferon and ribavirin; genotypes 1 and 4 less well.

Risk factors

- intravenous drug users
- patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

Pathophysiology

- hepatitis C is a RNA flavivirus
- incubation period: 6-9 weeks

The risk of Transmission:

- vertical transmission rate from mother to child is about 6%.
- sexual intercourse is probably less than 5% (in contrast to hepatitis B, sexual transmission is uncommon).
- needle stick injury is about 2%
 - > The risk is higher if there is coexistent HIV
- · breast feeding is not contraindicated in mothers with hepatitis C

Features

- after exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis
- Chronic hepatitis C is a very common cause of minor elevations in serum transaminases. Other liver function tests can be entirely normal

Diagnosis

- first → Arrange an anti-HCV antibody test
- HCV RNA tests are normally only ordered following a positive antibody test.

Associations

- · chronic hepatitis C associated with insulin resistance
- insulin sensitising drugs may improve response to anti-viral therapy

Extrahepatic association of hepatitis C

- Sjögren's syndrome
- dermatologic
 - Porphyria cutanea tarda
 - Lichen planus
- hematologic
 - Cryoglobulinaemia (mixed essential type)
 - myeloma and monoclonal gammopathies
 - non-Hodgkin lymphoma.
 - > immune thrombocytopenia,
 - > autoimmune hemolytic anemia
- renal
 - > membranoproliferative glomerulonephritis (more common)
 - Membranous glomerulonephritis (less common)

Complications

- chronic infection (80-85%)
- cirrhosis (20-30% of those with chronic disease)
- hepatocellular cancer
- cryoglobulinaemia

porphyria cutanea tarda (PCT)

Management of chronic infection

- chronic hepatitis C is defined as infection that lasts for more than 6 months.
- Combination therapy
 - > interferon-alfa and ribavirin
 - recommended for those with moderate-sever disease
 - (histological diagnosis of significant scarring and/or significant necrotic inflammation).
 - In cases where a liver biopsy carries a high risk (e.g. haemophilia), treatment can be initiated without histological confirmation.
 - currently a combination of pegylated interferon-alpha, ribavirin and a protease inhibitor (e.g. boceprevir, simprevir and telaprevir) is used
 - Genotype 1 hepatitis C have low rates of viral clearance with dual interferon and ribavirin therapy alone. the recommended duration of therapy is 48 weeks

Ledipasvir/sofosbuvir

- modern anti-hepatitis C antivirals, which work via inhibition of NS5A and NS5B
- can be used without ribavirin or interferon and hence lend themselves well to treatment of hepatitis C in the context of mixed cryoglobulinaemia.
- Because they can be used without interferon, they do not increase renal inflammation and reduce the viral load, impacting positively on progression of renal impairment.
- · Duration of treatment:
 - ➤ The effectiveness of antiviral treatment depends on the viral genotype; the response is generally better in people infected with genotypes 2 or 3 than in those infected with genotypes 1, 4, 5 or 6.
 - The recommended treatment duration is 24 weeks (genotypes 2 or 3) or 48 weeks (all other genotypes)
 - Both treatment-naïve (new) patients and those who have relapsed following initial response to interferon-alfa should be considered <u>for 6 months</u> of combination therapy.
- · Cure rates:
 - cure rates are now approaching 90%, including for some strains which have been previously difficult to treat
- The aim of treatment:
 - the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy
- Contra-indications:
 - > treatment is not generally recommended in those patients who consume large quantities of alcohol, given the increased risk of liver damage.
- Treatment follow-up:
 - the best way to assess response to treatment → Viral load
- Relapses
 - > relapse occurs in approximately 5% of people after 5 years.

Complications of treatment

- Ribavirin side-effects:
 - haemolytic anaemia,
 - > cough,
 - teratogenicity
 - Women should not become pregnant within 6 months of stopping ribavirin
- interferon alpha side-effects:
 - > flu-like symptoms,
 - fatigue,

- > depression.
 - Peginterferon alfa 2a and 2b are contraindicated in severe psychiatric conditions.
- leukopenia, thrombocytopenia.
 - close monitoring of FBC is recommended, with initial review after 4 weeks of therapy.

Factors Associated with Accelerated Fibrosis Progression			
Host	Viral		
Nonmodifiable Fibrosis stage Inflammation grade Older age at time of infection Male sex Organ transplant	 Genotype 3 infection Coinfection with hepatitis B virus or HIV 		
Modifiable Alcohol consumption Nonalcoholic fatty liver disease Obesity Insulin resistance			

MRCPUK-part-2-march-2018: A patient with H/O IV drug abuse, deteriorating renal function, spider naevi consistent with chronic liver disease, and the purpuric rash. Hepatitis C is positive. is the most appropriate intervention?

- → Ledipasvir/sofosbuvir
 - Δ hepatitis C with mixed cryoglobulinaemia
 - do not increase renal impairment
 - Ribavirin is less effective than NS5A and NS5B inhibition

Extrahepatic manifestations of chronic HCV infection: (PEN-DG)

- Porphyria cutanea tarda
- Essential mixed cryoglobulinemia
- Non-Hodgkin's lymphoma
- Diabetes mellitus
- Glomerulonephritis

Hepatitis D

Hepatitis D virus infection can only occur with coexistent hepatitis B infection.

Virology

- Hepatitis **D** is a single stranded **RNA** delta virus
- It is an incomplete RNA virus that requires hepatitis B surface antigen to complete its replication and transmission cycle.
- It is transmitted in a similar fashion to hepatitis B (exchange of bodily fluids) and patients may be infected with hepatitis B and hepatitis D at the same time.

Hepatitis D terminology:

- Co-infection:
 - > Hepatitis B and Hepatitis D infection at the same time.
- Superinfection:
 - a hepatitis B surface antigen positive patient subsequently develops a hepatitis D infection.
 - Superinfection is associated with high risk of fulminant hepatitis, chronic hepatitis status and cirrhosis.

Diagnosis

• made via reverse polymerase chain reaction of hepatitis D RNA.

Treatment

• Interferon is currently used as treatment, but with a poor evidence base.

Hepatitis E

Severe hepatitis in a pregnant woman - think hepatitis E

Virology

- RNA hepevirus
- · spread by the faecal-oral route
- incubation period: 3-8 weeks

Epidemiology

• common in Central and South-East Asia, North and West Africa, and in Mexico

Features

- causes a similar disease to hepatitis A,
- liver biopsy
 - Marked cholestasis is a hallmark histological finding in hepatitis E virus infection.
 - > Other liver biopsy features of a hepatitis E patient shows <u>patchy necrosis</u>

Management

- supportive
- In general, hepatitis E is a self-limiting viral infection followed by recovery. Prolonged viraemia or faecal shedding are unusual
- a vaccine is currently in development, but is not yet in widespread use

Prognosis

- does not result in a carrier state
- carries a significant mortality (about 20%) during pregnancy
- · does not cause chronic disease or an increased risk of hepatocellular cancer

Hepatitis histology

- hepatitis E → Marked cholestasis
- chronic hepatitis → Ground-glass hepatocytes (large hepatocytes containing surface antigen).
- Hepatitis A → Hepatocyte swelling, monocyte infiltration, and Councilman bodies
- hepatitis B → shows a granular eosinophilic "ground glass" appearance; cytotoxic T-cells mediate damage.
- hepatitis C → <u>Lymphoid</u> aggregates and a marked increase in the activation of sinusoidal lining cells
- hepatitis D → Microvesicular steatosis

Colorectal conditions

Colorectal cancer (CRC)

Endometrial cancer is the second most common association of HNPCC after colorectal cancer

Epidemiology

- Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths
- Adenocarcinomas comprise the vast majority (98%) of colon and rectal cancers
- Location of cancer (averages)
 - rectal: 40%
 - > sigmoid: 30%
 - descending colon: 5%
 - transverse colon: 10%
 - ascending colon and caecum: 15%

Risk factors

- · Colorectal adenomas
- · Family history
- Hereditary syndromes
 - > Familial adenomatous polyposis: 100% risk by age 40
 - ➤ Hereditary nonpolyposis colorectal cancer (HNPCC): 80% progress to CRC.
- Conditions associated with an increased risk of colorectal cancer
 - > Inflammatory bowel disease (IBD): ulcerative colitis and Crohn's disease
 - Endocarditis and bacteremia due to Streptococcus gallolyticus is associated with CRC.
 - Bovis in the Blood = Cancer in the Colon.
 - Acromegaly
 - Diet and lifestyle
 - > Smoking
 - > Alcohol consumption
 - > Obesity
 - Processed meat; high-fat, low-fiber diets
- Older age

Protective factors

- Physical activity
- Diet rich in fiber and vegetables and lower in meat
- Long-term use of aspirin and other NSAIDs

Risks for colorectal carcinoma

Population risk	1 in 40
One first-degree relative more than 45 years old	1 in 17
One first-degree plus one second-degree relative	1 in 12
Two first-degree relatives	1 in 6
Familial polyposis	1 in 2

Which drugs may reduce the risk of colon cancer?

- **⇒** Vitamin D
- **⇒** Aspirin and NSAID

Types

- There are three types of colon cancer:
 - 1. Sporadic (95%)
 - 2. Hereditary non-polyposis colorectal carcinoma (HNPCC, 5%)
 - 3. Familial adenomatous polyposis (FAP, <1%)
- Sporadic colon cancer
 - > may be due to a series of genetic mutations. For example:
 - allelic loss of the APC gene → more than half of colon cancers
 - further gene abnormalities e.g.
 - ❖ activation of the K-ras oncogene,
 - RAS is an intracellular signaling molecular that acts downstream of the epidermal growth factor receptor (EGFR) to stimulate cell division and growth
 - ⇒ present in 30-50% of colorectal cancers
 - ⇒ associated with failure to respond to EGFR based therapies such as the monoclonal antibodies Cetuximab and Panitumumab.
 - The presence of a KRAS mutation is a contraindication to treatment with these agents.
 - Which histopathological subtypes is essential for successful treatment with <u>cetuximab</u>?
 - K-Ras wild type
 - Cetuximab is licensed by NICE in metastatic colorectal cancer for K-Ras wild type proven patients who require downstaging prior to surgical resection of liver metastatic disease.
 - always given in combination with chemotherapy
 - major side effect → acne type rash.
 - deletion of p53 and DCC tumour suppressor genes lead to invasive carcinoma
- Hereditary non-polyposis colorectal carcinoma (HNPCC)
 - also known as (Lynch syndrome)
 - autosomal dominant mutation of DNA mismatch repair genes with microsatellite instability.
 - most common form of inherited colon cancer.
 - Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive.
 - The most common genes involved are:
 - MSH2 (60% of cases) the function of this gene → DNA mismatch repair
 - MLH1 (30%)

- > Patients with HNPCC are also at a higher risk of other cancers, with endometrial cancer being the next most common association, after colon cancer.
- > The **Amsterdam criteria** are sometimes used to aid diagnosis:
 - at least 3 family members with colon cancer
 - the cases span at least two generations
 - at least one case diagnosed before the age of 50 years
- > Torre-Muir syndrome, a type of hereditary nonpolyposis colorectal cancer (HNPCC), is characterized by sebaceous adenomas.

These lesions are usually present on the face, near the eyes and forehead and appear as yellow papules/nodules.



sebaceous adenomas associated with Torre-Muir syndrome a type of HNPCC

- Polyp cancers represent T1 disease and have been sub-classified.
- The Haggitt system is used for pedunculated polyps and describes the deepest invasion of carcinoma cells within the polyp:
 - Level 1 is limited to the head of the polyp
 - Level 2 is extension into the neck
 - Level 3 is invasion of the stalk, and
 - Level 4 is invasion beyond the stalk but above the muscularis propria.
- The Kicuchi system describes the depth of invasion in sessile polyp cancers.

Familial adenomatous polyposis (FAP)

- > FAP is a rare autosomal dominant condition which leads to the formation of hundreds of polyps by the age of 30-40 years.
- > Patients inevitably develop carcinoma.
- It is due to a mutation in a tumour suppressor gene called adenomatous polyposis coli gene (APC), located on chromosome 5.
- ➤ Genetic testing can be done by analysing DNA from a patients white blood cells.
- > Patients generally have a total colectomy with ileo-anal pouch formation in their twenties
- > Patients with FAP are also at risk from duodenal tumours.
 - Oesophago-gastroduo-denoscopy (OGD) surveillance is recommended.
- A variant of FAP called **Gardner's syndrome** can also feature:
 - osteomas of the skull and mandible.
 - retinal pigmentation,
 - thyroid carcinoma
 - and epidermoid cysts on the skin

Carcinoembryonic antigen may be used to monitor for recurrence in patients post-operatively or to assess response to treatment in patients with metastatic disease

Features

- Colorectal cancer on the <u>left</u> side of the body typically presents with bright red rectal bleeding.
- Colorectal cancer on the <u>right</u> side of the body typically presents with iron deficiency anemia and melena.
 - Colorectal cancer is the most common cause of iron deficiency anemia in postmenopausal women or in men aged 50 or older.
- In the <u>descending</u> colon, colorectal cancer presents as colicky pain and hematochezia.
- Colorectal cancer on the <u>left</u> side of the body typically presents with obstruction.
- In the <u>ascending</u> colon, colorectal cancer presents as an exophytic mass with iron deficiency anemia and weight loss.

Colorectal cancer: screening

Colorectal cancer screening - PPV of FOB = 5 - 15%

Overview

- most cancers develop from adenomatous polyps. Screening for colorectal cancer has been shown to reduce mortality by 16%
- the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening
- eligible patients are sent faecal occult blood (FOB) tests through the post
- patients with a single positive results are offered a colonoscopy
- An uncertain or unclear result will result in a request to repeat up to a maximum of two
 further tests. Persistent unclear results require further investigation with consideration of
 colonoscopy.
- A negative faecal occult blood does not exclude an underlying diagnosis of colorectal cancer.
- Any patient with symptoms, irrespective of a negative faecal occult blood test, should be investigated for the possibility of underlying bowel cancer as appropriate.

At colonoscopy, approximately:

- 5 out of 10 patients will have a normal exam
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential
- 1 out of 10 patients will be found to have cancer

Streptococcus bovis bacteraemia and endocarditis is associated with **colon cancer** (in around half of cases). All patients should, therefore, undergo **colonoscopy**

Colorectal cancer: referral guidelines

NICE updated their referral guidelines in 2015. The following patients should be **referred urgently** (i.e. within 2 weeks) to colorectal services for investigation:

- patients >= 40 years with unexplained weight loss **AND** abdominal pain
- patients >= 50 years with unexplained rectal bleeding
- patients >= 60 years with iron deficiency anaemia **OR** change in bowel habit
- tests show occult blood in their faeces (see below)

An urgent referral (within 2 weeks) should be 'considered' if:

- there is a rectal or abdominal mass
- there is an unexplained anal mass or anal ulceration
- patients < 50 years with rectal bleeding AND any of the following unexplained symptoms/findings:

- -→ abdominal pain
- → change in bowel habit
- → weight loss
- -→ iron deficiency anaemia

Faecal Occult Blood Testing (FOBT)

This was one of the main changes in 2015. Remember that the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening.

In addition FOBT should be offered to:

- patients >= 50 years with unexplained abdominal pain **OR** weight loss
- patients < 60 years with changes in their bowel habit **OR** iron deficiency anaemia
- patients >= 60 years who have anaemia even in the absence of iron deficiency

Follow-up period for adenomatous colonic polyps

- The British Society of Gastroenterology (BSG) guidelines on the follow-up period for adenomatous colonic polyps includes:
 - > 5-year interval is indicated for low-risk patients
 - (one to two adenomas that are both small, ie <1 cm)
 - > 3-year follow up is recommended for medium-risk patients
 - (three to four adenomas or one or two adenomas where one adenoma bigger than or equal to 1 cm)
 - > 1-year follow-up is recommended for high-risk patients
 - (five or more small adenomas or more than three with at least one at or above 1 cm in size).

guidance for colonoscopic surveillance

Risk profile	Definition	Surveillance interval
low risk	1 to 2 adenomas that are both small, ie <1 cm)	5-year
intermediate risk	(3 to 4 adenomas or 1 or 2 adenomas where one adenoma ≥ 1 cm)	3-year
high risk	≥ 5 small adenomas or > 3 with at least one at or above 1 cm in size).	1-year

Post polypectomy follow-up:

- Polyps that are ≤10 mm in size can be removed in a single go with biopsy forceps or snares.
- The need for repeat colonoscopy following polypectomy applies to large sessile adenomas removed piecemeal (that is, multiple snares required).
 - Small areas of residual polyp can then be treated endoscopically, with a further check for complete eradication in two to three months.
 - India ink tattooing aids recognition of the polypectomy site at follow up.
 - > If extensive residual polyp is seen, surgical resection needs to be considered.
 - If there is complete healing of the polypectomy site, then there should be a colonoscopy at one year, to check for missed synchronous polyps, before returning to three yearly surveillance.

Stages

• The stages of colorectal cancer are based on the TNM staging system by the American Joint Committee for Cancer (AJCC).

TNM Staging	Corresponding Duke's Classification stage	Description
I	А	Tumor confined to intestinal wall (confined to the muscularis propria)
II	В	Infiltration into the visceral peritoneum, adjacent organs, or perirectal tissue
Ш	С	Lymph node involvement
IV	D	Distant metastases

AJCCC (American Joint Committee) Staging of Colorectal Cancer

	_		
Primary	v Tum	nor	(T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
Т3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

MO	No distant metastasis
M1	Distant metastasis
М1а	Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Residual tumour (R) classification exists in addition to the TNM classification and the histological grade (G):

- RX presence of residual tumour cannot be assessed
- R0 no residual tumour
- R1 microscopic residual tumour
- R2 macroscopic residual tumour.

Management: depends upon the stage.

- Stage I (Duke's A):
 - Definition
 - Carcinoma in situ limited to mucosa or submucosa (T1, N0, M0).
 - Management
 - surgery to remove the tumour.
 - Additional treatments are not usually needed.
 - > Follow-up
 - <u>Colonoscopy</u> indicated on an <u>annual</u> basis for the first 2 years, then this should be done 3-yearly
 - Faecal occult blood should be tested 6-monthly for the first 4 years and then once yearly
 - Carcinoembryonic antigen (CEA) can be used to monitor for recurrence if it is elevated initially
 - Prognosis
 - the five-year survival rate exceeds 90%.
- Stage II (Duke's B):
 - Definition
 - Cancer that extends into the muscularis (B1), into or through the serosa (B2).
 - Management
 - surgical removal of the tumour followed by radiotherapy.
 - Radiotherapy has been shown to reduce the rate of recurrence.
 - The role of adjuvant chemotherapy is less clear in Duke's B than in Duke's C (see below).
 - chemotherapy is not typically given as standard.
 - Prognosis
 - the five-year survival rate is 70% 80%
- Stage III (Duke's C):
 - Definition
 - Cancer that extends to regional lymph nodes (T1-4, N1, M0).
 - Management
 - surgery to remove the tumour,
 - chemotherapy with 5-FU and leucovorin
 - in some patients radiotherapy may also be needed (especially if the tumour is large and invading the tissue surrounding the colon).

- There is no role for adjuvant radiation therapy in patients with colon cancer.
- Adjuvant radiotherapy is useful in patients with rectal cancer in whom the risk for local recurrence is greater.
- Prognosis
 - The five-year survival rate is less than 60% (40 50%)
- Stage IV (Duke's D):
 - Definition
 - Cancer that has <u>metastasised</u> to distant sites (T1-4, N1-3, M1).
 - Management
 - Surgery to remove the tumour or to bypass an obstructing tumour,
 - Metastatic lesion resection:
 - ⇒ Colorectal carcinoma is one of the only oncological diseases where the presence of a metastatic deposit can be treated with curative intent.
 - ⇒ A solitary liver lesion should be surgically resected.
 - ⇒ In fact, the purpose of following patients with CEA is to identify patients with solitary metastatic lesions amenable to surgical resection.
 - palliative chemotherapy and/or radiotherapy for symptom relief;
 - Trans-arterial chemoembolization & Radiofrequency ablation are used as palliative procedures when the lesions are too numerous or large to resect.
 - use of new agents such as cetumixab (a recombinant human/mouse chimeric epidermal growth factor inhibitor) or bevacizumab (a recombinant human antivascular epidermal growth factor (VEGF) antibody).
 - Prognosis
 - Five-year survival is approximately 5%.

Radiation therapy is not a standard modality in the treatment of colon cancers

MRCPUK-part-1-January 2015 exam: A man has hereditary non-polyposis colorectal cancer secondary to a mutation in the MSH2 gene. which other cancers his daughter will most be at risk from? Endometrial cancer

Dysplastic colonic polyps

The British Society of Gastroenterology (BSG) published guidelines on the follow-up period for dysplastic colonic polyps in 2002:

- 5-year interval is indicated for low-risk patients (one to two adenomas that are both small, ie <1 cm)
- 3-year follow up is recommended for medium-risk patients (three to four adenomas or one or two adenomas where one adenoma bigger than or equal to 1 cm)
- 1-year follow-up is recommended for high-risk patients (five or more small adenomas or more than three with at least one at or above 1 cm in size).

Polyp characteristics: associated with a higher risk of malignant change:

- polyps greater than 1.5 cm, which are <u>sessile or flat</u>
- Histology demonstrating severe dysplasia, predominantly villous architecture or squamous metaplasia

Peutz-Jeghers syndrome

- Peutz-Jeghers syndrome is an autosomal dominant condition
- · Characterised by:
 - > numerous hamartomatous polyps in the gastrointestinal tract.
 - > pigmented freckles on the lips, face, palms and soles.
- Around 50% of patients will have died from a gastrointestinal tract cancer by the age of 60 years.
- incidence of 1:50.000 live births.

Genetics

- autosomal dominant
- responsible gene encodes serine threonine kinase LKB1 or STK11

Features

- hamartomatous polyps in GI tract (mainly small bowel)
- pigmented lesions on lips, oral mucosa, face, palms and soles
- · intestinal obstruction e.g. intussusception
- gastrointestinal bleeding

Management

- · conservative unless complications develop
- colonoscopy every two years after the age of 25 for evaluation of the presence of polyps and polypectomy.

<u>Cowden's syndrome</u> is an inherited condition resulting from a defect in the PTEN tumour suppressor gene. Hamartomatous polyps of the GI tract are often the first manifestation along with characteristic muco-cuteneous lesions such as oral mucosal papillomas, palmoplantar keratoses and trichilemmomas (benign tumours of hair follicles). The syndrome is important to diagnose early because of the high risk of malignancy, particularly of the breast and thyroid. Thyroid dysfunction is common even in the absence of cancer.

<u>Familial juvenile polyposis</u> also results in multiple polyps in the colon identical to those found in Cowden's syndrome but the associated oral lesions are absent.

Capsule endoscopy

- Capsule endoscopy is currently used in UK to identify the source of occult gastrointestinal bleeding when an OGD and colonoscopy and failed to show a cause.
- It is particularly useful for identifying pathology in the ileum.

Pseudomyxoma peritonei

- Pseudomyxoma peritonei is a rare mucinous tumour most commonly arising from the appendix.
- The disease is characterised by the accumulation of large amounts of mucinous material in the abdominal cavity.
- It is rare, with an incidence of 1-2/1,000,000 per year

Treatment

• usually surgical and consists of cytoreductive surgery (and often peritonectomy) combined with intra-peritoneal chemotherapy with mitomycin C.

Villous adenoma

Diarrhoea + hypokalaemia → villous adenoma

Overview

- Villous adenomas are colonic polyps with the potential for malignant transformation.
- They characteristically secrete large amounts of mucous, potentially resulting in electrolyte disturbances.
- often in the rectum and rectosigmoid,

Features: The vast majority are asymptomatic. Possible features:

- · non-specific lower gastrointestinal symptoms
- secretory diarrhoea may occur
- microcytic anaemia
- hypokalaemia

Carcinoid tumours

Carcinoid syndrome

Left-sided valvular lesions are not observed in carcinoid syndrome because the lung metabolizes serotonin (5-HT). Remember the symptoms of carcinoid syndrome as "Be FDR": Bronchospasm, Flushing, Diarrhoea, and Right-sided valvular lesions.

- Carcinoid syndrome occurs in only 5% of patients with carcinoid tumour
- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- The most common originating sites of carcinoid is the small bowel, particularly the ileum;
 - Around 55% of all carcinoid tumours arise from the GI tract.
 - the most common site of origin is the small bowel (45% of those arising within the GI tract).
 - Within the small bowel, the most common site of origin is the distal ileum.
- carcinoid tumors are the most common malignancy of the appendix.
- 5-HT, kinins, prostaglandins and other vasoactive substances are secreted.
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver
- the caecal-appendiceal region is the commonest location for a carcinoid primary.
- These tumours are slow growing

Features

- flushing (often earliest symptom) the most common feature (occurring in 85% of patients)
 often provoked by alcohol.
- diarrhoea (75%) and abdominal cramps in the majority of patients.
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
 Cardiac abnormalities develop in 50% of patients and consist of tricuspid regurgitation or pulmonary stenosis.
 - Fibrosis of the heart valves is a recognised feature
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example. Cushing's syndrome
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation

- urinary 5-HIAA
 - 24-hour urine collection for 5-hydroxy-indole-acetic acid (5-HIAA) excretion is greater than 0.3 mmol.
- plasma chromogranin A y
- Biopsy of the lesion show cells staining for chromogranin A on histology → consistent with a neuroendocrine tumour
- Octreotide scanning is positive in up to 85% of cases, however a negative scan does not rule out liver metastases.
- The liver should be imaged by high resolution CT with fine cuts or by USS.
 - > The sensitivity of USS may be increased by the use of microbubble contrast medium (levovist), which is available at some centres.
- Fasting gut hormones should be measured as neuroendocrine tumours may co-secrete other hormones such as VIP, which may contribute to the diarrhoea.

Management

- somatostatin analogues e.g. octreotide
 - Octreotide is less likely to be effective if octreotide scan negative, but other analogues such as lanreotide have different affinities for different somatostatin receptor subtypes, which may be present on the tumour.
- diarrhoea: cyproheptadine may help
- Other Symptomatic management may include hepatic embolisation, hepatic chemoembolisation and chemotherapy.
- echocardiography to screen for carcinoid heart disease (right-sided valvular lesions).

Prognosis

· generally good.

Gorlin syndrome causes:

- 1. gastric hamartomas,
- 2. basal cell carcinomas,
- 3. mandibular bone cysts.
- 4. intracranial calcification,
- 5. pits on the palms and soles.

Diverticular disease

- Diverticulosis → presence of diverticula which are asymptomatic.
- Diverticular disease → diverticula associated with symptoms → typically painless bleeding
- Diverticulitis → diverticular inflammation (fever, tachycardia) with or without localised symptoms and signs → painful, No bleeding

Overview

- Diverticula are bulging sacs that push outward on the colon wall.can occur anywhere in the colon, but most commonly form near the end of the colon on the left side (sigmoid colon).
- A diverticulum consists of a herniation of mucosa through the thickened colonic muscle.
- most common in industrialized countries where diets are lower in fiber and higher in processed carbohydrates.
- Diverticular disease is by far the commonest cause of severe fresh bleeding per rectum.

Causes: It is believed diverticula form when there is increased pressure in the colon

- Diets low in fiber cause hard stool and slower "transit time" through the colon, increasing pressure.
- repeated straining during bowel movements also increases pressure.

 Drugs: diuretics, and narcotic pain relievers, can increase constipation and increase pressure in the colon.

Epidemiology

- Approximately 50% of all people have diverticula by the time they are 50 years of age, and nearly 70% of all people have diverticula by the time they are 80 years of age
- Diverticular disease is rare in people younger than 40 years
- Disease is more virulent in young patients, with a high risk of recurrences or complications.
- The most common fistula is colovesicular and then colovaginal fistulas.

Risk factors

- The main risk factors are age over 50 years and low dietary fibre.
- · Obesity is an important risk factor in young people.
- Complicated diverticular disease has an increased frequency in:
 - > patients who smoke,
 - > use non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol,
 - and those who are obese and have low-fibre diets

Features

- Approximately 75% of people with diverticula have asymptomatic diverticulosis
- Pain is generally exacerbated by eating and diminished with defecation or flatus.
- Other symptoms, such as bloating, constipation or rectal bleeding, may also occur.

Diverticulitis

- Mechanism
 - may occur if some faeces get trapped and stagnate in a diverticulum, bacteria then multiply and cause infection.
- > Site of the pain
 - Generally, presents with left lower quadrant pain.
 - Asian patients have predominantly right-sided diverticula and will usually present with right lower quadrant pain.
- Pain may be intermittent or constant and may be associated with a change in bowel habits.
- > Fever and tachycardia are present in most patients
- One third of patients who develop diverticulitis will develop further complications (perforation, abscess, fistula, stricture/obstruction)

Diagnosis: → colonoscopy

- sensitivities and specificities for CT are significantly better than for contrast enemas.
- When an abscess is suspected, CT scanning is the best modality for making the diagnosis and following its course.
- Because of risk of perforation, endoscopy is generally avoided in initial assessment of the
 patient with acute diverticulitis.

Haemorrhage:

- Flexible sigmoidoscopy is an appropriate initial approach to rule out an obvious rectosigmoid lesion.
- If no cause is identified, further assessment with non-invasive (nuclear scintigraphy) or invasive (angiography, colonoscopy) techniques can be undertaken in an attempt to localise and treat the bleeding source.

Management

asymptomatic

- ➤ No treatment or follow-up needs
- there may be a prophylactic benefit of a high-fibre diet.
- The risk of perforation may be increased by the use of NSAIDs and long-term use of opioids.
- Calcium-channel blockers are associated with a reduction in diverticular perforation but

there is insufficient evidence to recommend their use.

Diverticulitis

- Broad-spectrum antibiotics to cover anaerobes and Gram-negative rods eg, coamoxiclav or a combination of ciprofloxacin and metronidazole (if allergic to penicillin).
- > Paracetamol should be used for pain.
- Recommend clear liquids only; gradually reintroduce solid food as symptoms improve over 2-3 days.
- > Review within 48 hours, or sooner if symptoms deteriorate. Hospital admission should be arranged if symptoms persist or deteriorate.
- Mesalazine has been shown to be more effective in improving the severity of symptoms, bowel habit, and in preventing symptomatic recurrence of diverticulitis, than antibiotics alone
- Most patients admitted with acute diverticulitis will respond to conservative treatment, but 15-30% will need surgery.
- The indications for surgery are:
 - Purulent or faecal peritonitis.
 - Uncontrolled sepsis.
 - Fistula.
 - Obstruction.
 - Inability to exclude carcinoma.
- CT-guided percutaneous drainage of abdominal abscesses is now used in preference to surgery when feasible.
- Risk of recurrent symptoms after an attack of acute diverticulitis is about one in three
- Recurrent attacks are less likely to respond to medical treatment and they have a high mortality rate.

Haemorrhage

- ➤ Haemorrhage ceases spontaneously in 70-80% of patients.. Subsequent colonoscopy should be performed to establish the source of the bleeding and to exclude neoplasia.
- Intra-arterial vasopressin at angiography can control haemorrhage in more than 90% of patients. The benefit is usually only temporary but may allow time to prepare the patient adequately for surgery.
- Angiographic embolisation of very distal bleeding branches is also effective and safe.
- Surgery in lower gastrointestinal bleeding is usually reserved until endoscopic or angiographic treatments fail.
- Segmental resection is most usually done if the bleeding site is clearly identified from a therapeutically unsuccessful angiographic or endoscopic procedure. In patients with persistent bleeding and no angiographic or endoscopic identification of a definite bleeding site, subtotal colectomy may be required.
- ➤ The chance of a third bleeding episode can be as high as 50%, so many authorities recommend surgical resection after a second bleeding episode.

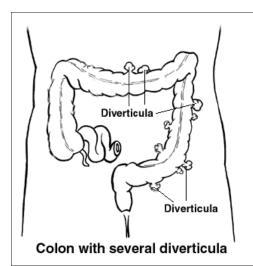
Prognosis

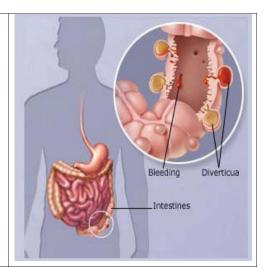
- Approximately three quarters of patients with anatomical diverticulosis remain asymptomatic.
- Most complications of diverticulitis are associated with the initial attack, after which the disease tends to run a benign course.
- Mortality and morbidity are related to complications of diverticulosis, which are mainly diverticulitis and lower gastrointestinal bleeding. These occur in 10-20% of patients with diverticulosis during their lifetime.

Prevention

Dietary fibre may prevent development of diverticular disease but, once symptoms develop, the benefit from fibre supplementation is unclear. Physical exercise has also been shown to help prevent the development of diverticular disease.

The presence of mixed Gram-negative and/or anaerobic organisms is highly suggestive of secondary peritonitis due to a perforated large bowel or appendicitis.





Meckel's diverticulum

- Meckel's diverticulum is the vestigial remnant of the omphalomesenteric duct.
- It is normally located in the terminal ileum within ~60 cm of the ileocaecal valve and it averages 6 cm in length.
- the diverticulum is frequently located near the ileocecal valve in the small bowel.
- In Meckel diverticulum, there is persistence of the vitelline duct, an embryologic structure
 necessary for receiving nutrients. When this structure persists, the Meckel diverticulum may
 contain ectopic tissue, such as the acid-secreting gastric mucosa
- Although it occurs much more commonly in children it is an important differential consideration for gastrointestinal bleed in adults.
- also quite common in Down's syndrome.

Features

- About 50% of these contain ectopic gastric mucosa, commonly leading to clinical presentations of peptic ulceration and haemorrhage.
- Other complications of Meckel's diverticulum include
 - Diverticulitis
 - Intussusception
 - Perforation
 - Obstruction.

Diagnosis

- Technetium 99m pertechnetate scintigraphy
 - ➤ Tc-99m pertechnetate accumulates in gastric mucosa and is the study of choice for identifying ectopic gastric mucosa in a Meckel's diverticulum.



The picture shows an excised Meckel's diverticulum.

Meckel diverticula: rule of 2's

- · occurs in 2% of the population,
- commonly located within 2-feet of the ileocecal valve,
- 2-inches in length,
- · commonly occurs before the age of two.

Intussusception

- Hirschsprung disease is aganglionosis of colon, causing obstruction. It usually presents in neonatal period.
- common cause of intestinal obstruction in children in general and in Down's syndrome in particular.
- There is a classic triad in intussusception of:
 - 1. acute abdominal pain,
 - 2. currant jelly stool and
 - 3. palpable abdominal mass, usually in right iliac fossa.

Aorto-enteric fistulae (AEF)

- known to occur following endovascular repair of abdominal aortic aneurysms (AAA) and secondary to aortic grafting of any kind, presumably because of mechanical forces of dislodged or migrating devices.
- May occur after aorto-bifemoral graft as treatment for peripheral vascular disease.
- Strongly positive faecal occult blood (FOB) suggests significant GI haemorrhage in spite of normal upper GI endoscopy.

<u>Angiodysplasia</u>

Angiodysplasia is associated with aortic stenosis

Definition

 Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia.

Epidemiology

- generally seen in elderly patients (≥ 60 years).
- the most common vascular lesion of the gastrointestinal tract
- Second most common cause of lower GI bleeding in patients >60 years of age.

Location of lesion

- · the most common site:
 - predominantly located in the proximal colon (77%) (located most commonly in the ascending colon and caecum)

Associations

- associated with aortic stenosis,
- In Heyde's syndrome, a syndrome of aortic valve stenosis and colonic angiodysplasia, a
 possible mechanism is the induction of von Willebrand's disease type IIA by the valvular
 stenosis.

Features

- may be asymptomatic,
- gastrointestinal bleeding (estimated incidence of active bleeding being about 10% of affected cases).

Diagnosis

- Colonoscopy
 - ➤ If the initial colonoscopy is negative, the most appropriate next investigation is → repeat colonoscopy.
 - Pick up of colonic angiodysplasia, (sensitivity), is only 80% by colonoscopy however, this is why it is advisable to move to a repeat colonoscopy.
 - Once two colonoscopies have taken place, moving to <u>capsule endoscopy is a usual next step.</u>
- The repeated negative upper and lower GI endoscopies suggest that small bowel
 angiodysplasia may be the cause, in an area which is difficult to image via conventional
 endoscopy. In this situation capsule endoscopy has a higher yield and would be the
 appropriate next step.
 - > The pathophysiology of angiodysplasia in this situation isn't known, although it may be due to changes in pressure within the mesenteric venous plexus, as the condition often resolves once the valve is treated.
- mesenteric angiography if acutely bleeding

Management

- Bleeding stops spontaneously in >90% of cases.
- endoscopic cautery or argon plasma coagulation
- · antifibrinolytics e.g. Tranexamic acid
- · oestrogens may also be used

Heyde's syndrome → gastrointestinal bleeding from angiodysplasia in the presence of aortic stenosis.

Angiodysplasia of the gastrointestinal tract

- Features:
 - can be silent or cause bleeding
 - most often detected in patients older than 60 years
 - typically present with occult blood loss
- Most common site → Right colon
- Associated conditions:
 - 1. end-stage kidney disease
 - 2. von Willebrand disease
 - 3. aortic stenosis
- Diagnosis → endoscopy
- Treatment :
 - if causes bleeding e.g. iron deficiency anaemia → endoscopic therapy
 - if found accidentally → do not treat

Anal fissure

Anal fissure - topical glyceryl trinitrate

Anal fissures are longitudinal or elliptical tears of the squamous lining of the distal anal canal. If present for less than 6 weeks they are defined as acute, and chronic if present for more than 6 weeks. Around 90% of anal fissures occur on the posterior midline

Management of an acute anal fissure (< 6 weeks)

- · dietary advice: high-fibre diet with high fluid intake
- bulk-forming laxatives are first line if not tolerated then lactulose should be tried
- lubricants such as petroleum jelly may be tried before defecation
- topical anaesthetics
- analgesia topical steroids do not provide significant relief

Management of a chronic anal fissure (> 6 weeks)

- · the above techniques should be continued
- topical glyceryl trinitrate (GTN) is first line treatment for a chronic anal fissure
- if topical GTN is not effective after 8 weeks then secondary referral should be considered for surgery or botulinum toxin

Anal fistula

- Goodsall's rule describes the likely location of the internal opening of a fistula-in-ano based on its external opening.
 - If the external opening is anterior to the 9-3 o'clock plane, then the fistula forms a direct radial tract and opens internally at the same clock face point.
 - If the external opening is posterior to this line then it will generally follow a more circuitous route opening at 6 o'clock.

Inflammatory bowel disease (IBD)

Crohn's disease

Definition

- Crohn's disease is a form of inflammatory bowel disease.
- Commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.

Epidemiology

- IBD is more common in white people than in African-Caribbean people or those of Asian origin.
- has a lower incidence in non-white races; people of Jewish origin are more prone to inflammatory bowel disease than non-Jews; and Ashkenazi Jews are at higher risk than Sephardic Jews.
- slightly more common in females (male to female ratio is 1:1.2)
- typically presents in late adolescence or early adulthood. The highest incidence of Crohn's disease in the 15–30 year age
- The ratio of Crohn's disease to ulcerative colitis varies between adults and children. In adults, the ratio of Crohn's disease to ulcerative colitis is 2:3, while the ratio in children is much higher (2.3:1).

Pathology

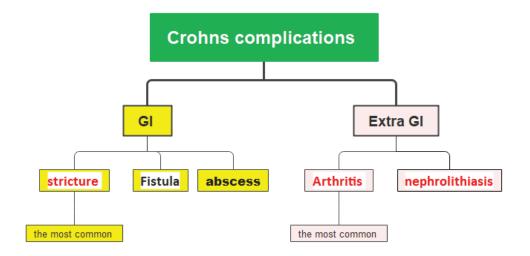
- cause is unknown but there is a strong genetic susceptibility
- inflammation occurs in all layers, down to the serosa. This is why patients with Crohn's are prone to strictures, fistulas and adhesions

Features

- non-specific symptoms such as weight loss and lethargy
- · diarrhoea:
 - > the most prominent symptom in adults.
 - Crohn's colitis may cause bloody diarrhea.
 - Nocturnal diarrhoea is indicative of organic disease and is typical of a <u>Crohn's</u> disease flare.
- abdominal pain:
 - > the most prominent symptom in children.
 - > often in the lower right quadrant
- perianal disease: e.g. Skin tags or ulcers
 - if the patient has sepsis secondary to a <u>perianal abscess</u>, due to underlying Crohn's disease. The priority is to delineate the <u>extent of the abscess</u> and potential fistula by an urgent pelvis MRI before draining it via Examination under anaesthesia (EUA).
 - the next best investigation to guide further management → <u>Immediate</u>
 MRI pelvis
 - CT is inferior to MRI in detecting perianal pathology
- An abdominal mass is often palpable in the presence of small bowel disease which can lead to Vitamin K malabsorption.
- extra-intestinal features are more common in patients with colitis or perianal disease

Extra-intestinal manifestations of IBD → A PIE SAC:

- Aphthous ulcers
- Pyoderma gangrenosum
- Iritis
- Erythema nodosum
- Sclerosing cholangitis
- Arthritis
- Clubbing of fingertips



Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

	Common to both Crohn's disease (CD) and Ulcerative colitis (UC)	Notes
Related to disease activity	 Aphthous oral ulcers Arthritis: pauciarticular, asymmetric Erythema nodosum Episcleritis Osteoporosis 	 the most common extra-intestinal feature in both CD and UC Arthritis more common in CD Episcleritis Interstitial lung disease
Unrelated to disease activity	 Arthritis: polyarticular, symmetric Uveitis Pyoderma gangrenosum Clubbing Primary sclerosing cholangitis 	more common in UC Primary sclerosing cholangitis Uveitis

Smoking in IBD

- Smoking associated with earlier age of onset of disease and more frequent need for immunosuppression among women with Crohn's disease but not men.
- Smoking cessation is associated with an increased risk of ulcerative colitis.

Investigation

Bloods

· C-reactive protein correlates well with disease activity

Faecal calprotectin

- Calprotectin is a protein belonging to the S100 family and occurring in large amounts in neutrophil granulocytes
- Increased faecal calprotectin indicates increased migration of neutrophils to intestinal mucosa
- \^ Calprotectin in stool is the direct consequence of neutrophil degranulation due to
 mucosal damage.

- The logical next step in excluding inflammatory bowel disease
- Recommended by NICE to distinguish between inflammatory bowel diseases and non-inflammatory bowel diseases, such as irritable bowel syndrome in people presenting with any of the following lower gastrointestinal symptoms for at least 6 weeks: abdominal pain or discomfort, bloating, or change in bowel habit.
- ↑↑ when there is any intestinal inflammation → Crohn's disease or ulcerative colitis.
- normal value is approximately 25 mg/kg.
- in IBS values may be slightly higher than those of healthy subjects, but in IBD significantly
 ↑↑
- Calprotectin exceeding 50 mg/kg should be considered positive → do endoscopy to confirm IBD
- Non-invasive screen for IBD
- Normal faecal calprotectin → makes IBD unlikely
- ↑↑ faecal calprotectin → drive further imaging

Stool culture

- should be performed first
- Even if the presentation is highly suggestive of inflammatory bowel disease. However, it is unforgivable not to do a stool culture in a case of diarrhoea and that should be the starting point before considering the other investigations

Endoscopy

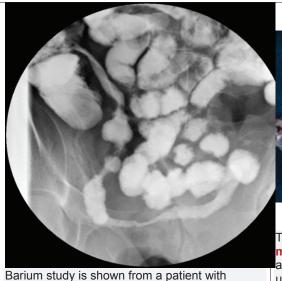
- colonoscopy is the investigation of choice
 - > Crohn's disease most typically affects the terminal ileum and proximal colon, therefore the investigation of choice would be ileo-colonoscopy.
 - > A flexible sigmoidoscopy may not identify any areas of disease.
- features suggest of Crohn's include deep ulcers, skip lesions

Histology

- · inflammation in all layers from mucosa to serosa
- goblet cells
- granulomas
- Patchy inflammation

Small bowel enema

- high sensitivity and specificity for examination of the terminal ileum
- · strictures: 'Kantor's string sign'
- proximal bowel dilation
- 'rose thorn' ulcers
- fistulae



Barium study is shown from a patient with worsening Crohn's disease. Long segment of narrowed terminal ileum in a 'string like' configuration in keeping with a long stricture segment. Termed 'Kantor's string sign'.

The picture shows the typical 'cobblestone mucosa' of Crohn's disease with isolated areas of normal mucosa surrounded by deep ulceration (ulcerative colitis does not result in such deep ulceration).

Thumb printing

 thumb printing is a predominantly radiological finding due to inflamed, oedematous folds of bowel as a result of mucosal oedema caused by inflammation. Thumb printing may be seen in either Crohn's disease or ulcerative colitis.

Management (NICE 2012)

· · · · · · · · · · · · · · · · · · ·	· ·	
	CD	UC
Inducing remission	• conventional glucocorticosteroids (oral, topical or I.V), OR • Budesonide (less effective and less side effect): (for mild to moderate + distal ileal, ileocaecal or right-sided colonic disease + conventional glucocorticosteroids are contraindicated, or not tolerated) OR • enteral nutrition (If any concern about growth SE of steroids e.g. in children) OR • aminosalicylate (less effective and less side effect): (for mild to moderate + conventional glucocorticosteroids are contraindicated, or not tolerated)	Mild & moderate UC 1st line: • Rectal & distal colitis → rectal (topical) Aminosalicylates is superior to rectal steroids • Proximal colitis → oral Aminosalicylates Sever UC → hospital → 1st line (1.V steroid)

2nd line → adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide (if:

- there are 2 or more inflammatory exacerbations in a 12-month period or
- the glucocorticosteroid dose cannot be tapered.

3rd line: add methotrexate to a conventional glucocorticosteroid or budesonide (If azathioprine or mercaptopurine not tolerated, or in whom TPMT activity is deficient).

Severe form

1st line : conventional glucocorticosteroids

2nd line: (not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments) Infliximab or adalimumab

(severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3 to 4 or more) diarrhoeal stools daily.)

2nd line → oral prednisolone

Maintaining remission

Stop smoking

1st line → azathioprine or
mercaptopurine (or methotrexate

ONLY if needed to induce remission)

2nd line (if azathioprine or
mercaptopurine not tolerated or not
appropriate) → methotrexate
post-surgery → azathioprine in
combination with up to 3 months'
postoperative metronidazole, OR
azathioprine alone for people who
cannot tolerate metronidazole

- oral 5-ASA e.g. mesalazine
- azathioprine and mercaptopurine (methotrexate is NOT recommended for UC)

Inducing remission in Crohn's disease: 2 nd , 3 rd lines and severe form (NICE 2019) (PassOnExam)			
	Case	Treatment	
2 nd line	≥ 2 exacerbations in a 12-month period OR the glucocorticosteroid dose cannot be tapered.	Add Azathioprine OR Mercaptopurine to a conventional glucocorticosteroid or budesonide	
3 rd line	 Azathioprine or mercaptopurine not tolerated OR in whom TPMT activity is deficient 	add Methotrexate to a conventional glucocorticosteroid or budesonide	
Severe form	very poor general health + one or more symptoms such as weight loss, fever, severe abdominal pain and ≥ 3 diarrhoeal stools daily.	1st line: conventional glucocorticosteroids 2nd line: (not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments) Infliximab or adalimumab	

	Crohn's disease		
	Maintaining remission (NICE 2019)		
1st line	Azathioprine OR mercaptopurine		
	Methotrexate ONLY if needed to		
	induce remission.		
2 nd line	Methotrexate		
post-surgery	Azathioprine + in combination with		
(complete	up to 3 months' postoperative		
macroscopic	metronidazole, OR		
resection)	azathioprine alone for people who		
	cannot tolerate metronidazole		

General points

- patients should be strongly advised to stop smoking
- some studies suggest an increased risk of relapse secondary to NSAIDs and the combined oral contraceptive pill but the evidence is patchy
- dietary advice
 - Short-term use of TPN may be helpful in severe cases
 - > There is a significant portion of Crohn's patients who are lactose intolerant, and hence a dairy free diet may reduce the frequency of diarrhoea.

Inducing remission

- <u>glucocorticoids</u> (oral, topical or intravenous) are generally used to induce remission. Budesonide is an alternative in a subgroup of patients
- enteral feeding with an elemental diet may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children)
- 5-ASA drugs (e.g. mesalazine) are used second-line to glucocorticoids but are not as effective
- azathioprine or mercaptopurine* may be used as an add-on medication to induce remission but is not used as monotherapy. Methotrexate is an alternative to azathioprine
- infliximab is useful in refractory disease and fistulating Crohn's. Patients typically continue on azathioprine or methotrexate
- metronidazole is often used for **isolated peri-anal** disease

After a diagnosis of small bowel Crohn's disease, a patient asked for therapy that is as **effective as a course of corticosteroids, but with a better adverse event** profile. What would you recommend?

- → Defined formula diet
 - One study showed corticosteroids to have an 80% short-term remission rate, while sole-source liquid diets had a 60% remission rate.
 - However, the rate of remission rose to 80% with sole-source liquid diets for those who were able to tolerate a course of therapy.

Maintaining remission

- stopping smoking is a priority
 - (remember: smoking makes Crohn's worse, but may help ulcerative colitis)
- **first-line** → azathioprine or mercaptopurine
 - *assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine
- **second-line** → methotrexate
- if a patient has had previous surgery → 5-ASA drugs (e.g. mesalazine) should be considered

Surgery

- around 80% of patients with Crohn's disease will eventually have surgery
 - > Side effects
 - Bile salt malabsorption
 - ❖ Loss of the terminal ileum frequently leads to → bile salt malabsorption
 - commonly presents with watery diarrhoea.
 - diagnosis can be confirmed with a SEHCAT scan.
 - treatment with the bile salt chelator cholestyramine

Treatment during pregnancy

- For relapse during pregnancy
 - > 1st line > Prednisolone is the most appropriate initial treatment
 - \triangleright 2nd line (in patients who not responds to corticosteroids) \rightarrow Infliximab
 - Infliximab is thought to be low risk in pregnancy although it does cross the placenta.
 - Patients on maintenance infliximab therapy should stop treatment by week 26 gestation.
 - In patients who require treatment in the last trimester, live vaccines should be avoided in the newborn for the first 6 months.
- For maintenance therapy → azathioprine or 6MP

Complications: There are 3 main serious intestinal complications in Crohn's disease:

- 1. Stricture (narrowing) of the bowel → intestinal obstruction
- **2.** Fistulas, which are abnormal connections between sections of the bowel, or between the bowel and bladder.
- 3. colorectal cancer

Prognosis: (Nice 2013)

Prognostic feature	Crohn's disease	ulcerative colitis
prolonged remission	Only 10%	50%
surgery within 10 years of diagnosis	50%	20–30%
risk of mortality compared with the general population	slightly increased	Not increased
General outlook	worse than ulcerative colitis	Better than Crohn's

Renal calculi are increased in Crohn's due to a mixture of dehydration and increased oxalate due to small bowel pathology and previous surgery. (Non-contrast helical CT abdomen is the investigation of choice for suspected renal calculi.)

Crohn's-like enterocolitis with mycophenolate mofetil

- Reported in renal transplant patients who have received mycophenolate mofetil.
- Investigations will reveal mucosal ulceration and skip lesions ordinarily seen in Crohn's.
- Treatment → Withdrawal of mycophenolate → resolution of symptoms

Ulcerative colitis (Nice guidelines 2013)

Ulcerative colitis - the rectum is the most common site affected

- Ulcerative colitis (UC) is a form of inflammatory bowel disease.
- Inflammation always starts at rectum (hence it is the most common site for UC),
- never spreads beyond ileocaecal valve and is continuous.
- The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.

Features

The initial presentation is usually following insidious and intermittent symptoms:

- bloody diarrhoea
- urgency
- · tenesmus
- abdominal pain, particularly in the left lower quadrant
- extra-intestinal features (see below)

Severity of ulcerative colitis (Mild, moderate and severe)

- In adults the severity criteria are based on the Truelove and Witts' severity index
- In children (≤ 11 years) and young people (12 to 17 years) these categories are based on the Paediatric Ulcerative Colitis Activity Index (PUCAI)

Truelove and Witts' severity index

	Mild	Moderate	Severe
Bowel movements (no. per day)	< 4		≥ 6 + at least one of the features of systemic upset (Pyrexia, Pulse > 90, anaemia, ↑ESR)
Blood in stools	small amounts	Between mild and severe	Visible blood
Pyrexia (> 37.8°C)	No	No	Yes

Pulse > 90 bpm	No	No	Yes
Anaemia Haemoglobin <105 g/L	No	No	Yes
ESR	≤ 30	≤ 30	> 30
C reactive protein	≤ 30	≤ 30	>30

Pathology

- · red, raw mucosa, bleeds easily
- no inflammation beyond submucosa (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- neutrophils migrate through the walls of glands to form crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- · granulomas are infrequent

Barium enema

- · loss of haustrations
- · superficial ulceration, 'pseudopolyps'
- · long standing disease: colon is narrow and short -'drainpipe colon'



Abdominal x-ray from a patient with ulcerative colitis showing **lead pipe appearance** of the colon (red arrows). Ankylosis of the left sacroiliac joint and partial ankylosis on the right (yellow arrow), reinforcing the link with sacroilitis.

Ulcerative colitis: flares

- Non-steroidal anti-inflammatory drugs (NSAIDs) cause flares of inflammatory bowel disease
- Cytomegalovirus is an uncommon cause of non-responsive colitis.

Flares of ulcerative colitis are usually classified as either mild, moderate or severe:

Mild	Moderate	Severe
 < 4 stools/day, with or without blood 	4-6 stools/day, with minimal systemic	>6 bloody stools per day, containing bloodEvidence of systemic disturbance, e.g.

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Mild	Moderate	Severe
No systemic disturbance Normal ESR and C-reactive protein values	disturbance	 fever tachycardia abdominal tenderness, distension or reduced bowel sounds anaemia hypoalbuminaemia

Patients with evidence of severe disease should be admitted to hospital.

Risk factors for the precipitation of toxic colonic dilatation

ulcerative colitis identify the following as risk factors for the precipitation of toxic colonic dilatation:

- Hvpokalaemia
- Hypomagnesaemia
- Under-treatment
- Purgative bowel preparations for colonoscopy
- Non-steroidals
- Opioids
- Anti-cholinergics, and
- · Anti-diarrhoeal agents.
- inappropriately delayed

Ulcerative colitis: management (NICE 2013)

Treatment can be divided into inducing and maintaining remission..

Inducing remission

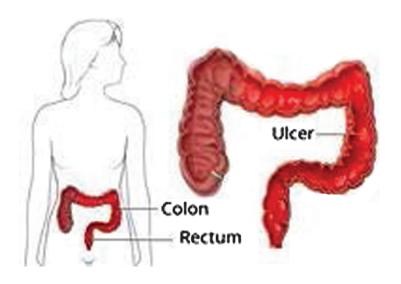
- treatment depends on the extent and severity of disease
- rectal (topical) aminosalicylates or steroids: for distal colitis rectal mesalazine has been shown to be superior to rectal steroids and oral aminosalicylates
- oral aminosalicylates
- oral prednisolone is usually used second-line for patients who fail to respond to aminosalicylates. NICE recommend waiting around 4 weeks before deciding if first-line treatment has failed
- severe colitis should be treated in hospital. Intravenous steroids are usually given first-line

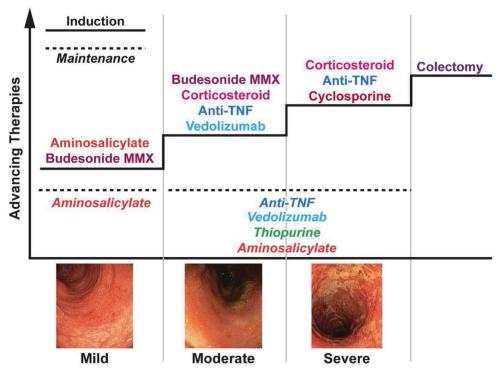
Maintaining remission

- · oral aminosalicylates e.g. mesalazine
- azathioprine and mercaptopurine
- methotrexate is not recommended for the management of UC (in contrast to Crohn's disease)
- there is some evidence that probiotics may prevent relapse in patients with mild to moderate disease

Inactive (quiescent) colitis:

- . (ESR) is not raised in quiescent UC
- If the ESR, CRP and platelet counts are not raised, indicating that the patient's symptoms are not due to active disease.
- Neutrophilic infiltrate is present if disease is active
 - > Involves epithelium of surface and crypts
 - > Frequently forms crypt abscesses





Step-up approach to treatment based on disease severity. CLINICAL OVERVIEW Ulcerative colitis. Elsevier Point of Care. Updated December 21, 2019.

 $\frac{\text{https://www.clinicalkey.com/\#!/content/clinical_overview/67-s2.0-0c7ff1f6-29bc-46f1-a7b7-4bcf12316903?scrollTo=\%2367-s2.0-0c7ff1f6-29bc-46f1-a7b7-4bcf12316903-99c15915-a11a-451d-9cb0-8db17e1930c9-annotated}$

www.clinicalkey.com

Ulcerative colitis: colorectal cancer

Overview

- risk of colorectal cancer is significantly higher than that of the general population although studies report widely varying rates
- the increased risk is mainly related to chronic inflammation
- worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- · lesions may be multifocal

Factors increasing risk of cancer

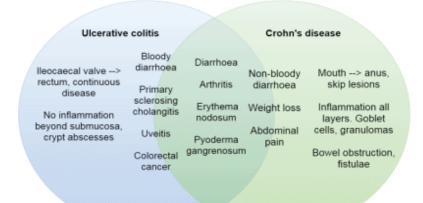
- disease duration > 10 years
- patients with pancolitis
- onset before 15 years old
- · unremitting disease
- poor compliance to treatment

Colonoscopy surveillance & Risk stratification of IBD

- All patients with a diagnosis of colitis should have a screening colonoscopy 10 years after index presentation, preferably when they are in remission.
- patients should be decided following risk stratification.
 - ▶ Lower risk → 5-year follow up colonoscopy
 - Extensive colitis with no active endoscopic/histological inflammation
 - left sided colitis
 - Crohn's colitis of <50% colon
 - ➤ Intermediate risk → 3-year colonoscopy
 - Extensive colitis with mild active endoscopy/histological inflammation
 - post-inflammatory polyps
 - OR family history of colorectal cancer in a first degree relative aged 50 or over
 - ⇒ Higher risk → 1 year follow up colonoscopy
 - Extensive colitis with moderate/severe active endoscopic/histological inflammation
 - stricture in past 5 years
 - dysplasia in past 5 years declining surgery
 - primary sclerosing cholangitis / transplant for primary sclerosing cholangitis
 - family history of colorectal cancer in first degree relatives aged <50 years

Inflammatory bowel disease: key differences

- The two main types of inflammatory bowel disease are Crohn's disease and Ulcerative colitis.
- They have many similarities in terms of presenting symptoms, investigation findings and management options.
- There are however some key differences which are highlighted in table below:



Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

	Crohn's disease (CD)	Ulcerative colitis (UC)	
Features	Diarrhoea usually non-bloody Weight loss more prominent Upper gastrointestinal symptoms, mouth ulcers, perianal disease Abdominal mass palpable in the right iliac fossa	Bloody diarrhoea more common Abdominal pain in the left lower quadrant Tenesmus	
Extra- intestinal	Gallstones are more common secondary to reduced bile acid reabsorption Oxalate renal stones*	Primary sclerosing cholangitis more common	
Complications	Obstruction, fistula, colorectal cancer	Risk of colorectal cancer high in UC than CD	
Pathology	Lesions may be seen anywhere from the mouth to anus	Inflammation always starts at rectum and never spreads beyond ileocaecal valve Continuous disease	
	Skip lesions may be present		
Histology	Inflammation in all layers from mucosa to serosa increased goblet cells granulomas	No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria • neutrophils migrate through the walls of glands to form crypt abscesses • depletion of goblet cells and mucin from gland epithelium • granulomas are infrequent	

	Crohn's disease (CD)	Ulcerative colitis (UC)
Endoscopy	Deep ulcers, skip lesions - 'cobble-stone' appearance Widespread ulceration with pre adjacent mucosa which has the of polyps ('pseudopolyps')	
Radiology	Small bowel enema	Barium enema loss of haustrations superficial ulceration, 'pseudopolyps' long standing disease: colon is narrow and short -'drainpipe colon'

^{*}impaired bile acid reabsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

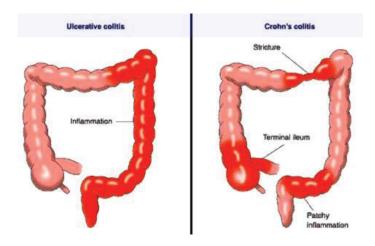
IBD: histology

This histological differences between Crohn's and ulcerative colitis are summarised below: **Crohn's**

- inflammation occurs in all layers, down to the serosa. This predisposes to strictures, fistulas and adhesions
- oedema of mucosa and submucosa, combined with deep fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern
- · lymphoid aggregates
- non-caseating granulomas

Ulcerative colitis

- inflammation in mucosa and submucosa only (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- · inflammatory cell infiltrate in lamina propria
- crypt abscesses
- · depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent



feature	Ulcerative colitis	Crohn's
Most common site	Rectum	Terminal ileum
Distribution	Rectum to colon "backwash" ileitis	Mouth to anus
Spread	Continuous	Discontinuity "skip" lesions
Gross features	Extensive ulcerationPseudo-polyps	☐ Focal aphthous ulcers with intervening normal mucosa ☐ Linear fissures ☐ Cobblestone appearance ☐ Thickened bowel wall lihitis plastic" ☐ Creeping fat
Micro	 Crypt abscess 	Noncaseating granulomas
Inflammation	 Limited to mucosa and submucosa 	Transmural
Complication	Toxic megacolon	☐ Strictures ☐ String sign on barium study ☐ Obstruction ☐ Abscess ☐ Fistula ☐ Sinus tract
Genetic Association	HLA-B27	
Extraintestinal manifestation	Common	Uncommon
Cancer risk	5-25%	Slight 1-3%
Presentation	Bloody diarrhea	Variable : Pain, diarrhea, weight loss

Pseudopolyps are seen in both ulcerative colitis and Crohn's disease.

history of previously well-controlled ulcerative colitis, treated with mesalazine 1.2 g daily. presented with a 5-day history of increasing bowel frequency. A diagnosis of active proctitis was made. What is the most appropriate treatment?

⇒ increase mesalazine dosage

Microscopic colitis (Collagenous colitis and Lymphocytic colitis)

- Microscopic colitis (MC) is an inflammatory condition of the colon that presents with two subtypes: collagenous (CC) and lymphocytic colitis (LC).
- Both types of MC present with watery diarrhea, and normal endoscopic findings. Differentiation is made by histological examination but treatment is the same.
- Risk factors for MC are female gender, higher age, concomitant autoimmune disease, past and current diagnosis of malignancy of organ transplant
 - ⇒ Among all autoimmune disorders, celiac disease appears to have the strongest association.
 - The use of proton pump inhibitors (PPIs) (lansoprazole), low dose aspirin, β-blockers, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), statins, and bisphosphonates have all been associated with MC

Diagnosis

- ⇒ histological evaluation through lower endoscopy.
 - The histology found in MC (both CC and LC) demonstrates lymphocytic infiltration of the lamina propria and the epithelium.
 - CC differs from LC in that there is marked thickening of the subepithelial layer.
 - Intraepithelial lymphocytosis (IEL) can be found in both CC and LC, but is more pronounced in LC: ≥ 20 intraepithelial lymphocyte per 100 surface epithelial cells are needed to make the diagnosis
- Both MC respond well to oral budesonide.
- Prognosis is good with resolution of symptoms after medical therapy.
- 38% of the patients achieve spontaneous remission with either no treatment or with simple anti-diarrheals.

Histological features of collagenous colitis and lymphocytic colitis

	Collagenous colitis	Lymphocytic colitis	
Lamina propria	Lymphocytic infiltration of the lamina propria with little or no damage in mucosal architecture		
Subepithelial layer	Thickening of subepithelial layer > 10 µm	Subepithelial collagen layer not present or < 10 µm	
Intraepithelial	Intraepithelial lymphocytosis could be present, but necessary for the diagnosis	Intraepithelial lymphocytosis (≥ 20 IEL per 100 surface epithelial cells)	

Management

- ⇒ discontinue any potentially offending drug.
- ⇒ mild and intermittent symptoms can be treated with anti-diarrheal medication (loperamide).
- □ moderate to severe symptoms: only budesonide has strong supporting evidence and should be the first-line treatment in inducing and maintaining clinical remission in both CC and LC
 - Prednisone is an alternative corticosteroid that has shown some efficacy in treating MC. however it is less effective than budesonide.

Rule out infectious process and other diseases

Obtain histololgical evaluation via colonoscopy to confirm diagnosis

Discontinue medications associated with MC

Trial of anti-diarrheal medications (mild)

Trial of budesonide in tapering dose

Collagenous colitis

- Collagenous colitis is one of the forms of microscopic colitis, i.e. a condition in which the colon appears normal on colonoscopy, but where the diagnosis is made based on the abnormal histology of colonic biopsies.
- predominantly affects women (male: female of 1: 4) in the fifth and sixth decades of life.
- · aetiology is unknown,
- · although associated with
 - ⇒ several medications in particular, non-steroidal anti-inflammatory drugs
 - ⇒ coeliac disease and other autoimmune disorders.
- chronic watery diarrhoea (which tends to be worse during the day than at night), and is also often accompanied by crampy, diffuse abdominal pain.
- normal blood tests, radiological and macroscopic appearances.
- The diagnosis is made based on the typical histological appearances of a thickened subepithelial collagen band, a moderate inflammatory cell infiltrate, and an increase in intraepithelial lymphocytes.
- Treatments include antidiarrhoeal agents (such as Loperamide), 5-aminosalicyclate drugs, corticosteroids, and bile acid sequestrants, all of which are variably effective.

Lymphocytic colitis

- Associations
 - ⇒ occur in patients with other forms of GI pathology, including Crohn's and Coeliac.
 - Sertraline also appears to be associated with the development of lymphocytic colitis.
- Management

- ⇒ Withdrawal of the offending agent is preferable,
- ⇒ loperamide is often used as a first line therapy to reduce the severity of diarrhoea, with cholestyramine an alternative if there is bile salt malabsorption.
- ⇒ Other alternatives include immune modulating agents such as azathioprine, although a response to therapy may take many months to appear.

Toxic megacolon (Toxic dilatation of the colon)

DON'T GIVE ANTI-DIARRHEAL Rx FOR ACUTE COLLITIS → TOXIC MEGACOLON

Flexible sigmoidoscopy is the best investigation - safer than colonoscopy (relative contraindication in active colitis), allowing biopsies to be taken and the viewing of a possible pseudomembrane. Occasionally the mucosa has a characteristic appearance.



Toxic megacolon is characterized by extreme inflammation and distention of the colon. Common symptoms are pain, distention of the abdomen, fever, rapid heart rate, and dehydration. This is a life-threatening complication that requires immediate medical treatment.

- Usually associated with severe colitis.
 - ⇒ usually due to severe UC but also with Crohn's colitis and rarely ischaemic or infective colitis
- The transverse or right colon is usually the most dilated part in toxic megacolon, often greater than 6 cm and occasionally up to 15 cm on supine films.

Diagnostic criteria

toxic megacolon → transverse colon dilatation ≥ 6 cm + signs of systemic toxicity.

- Radiographic evidence of colonic distension
- plus at least three of the following:
 - > Fever >38.6°C
 - ➤ Heart rate >120 beats per minute (The most reliable sign is the pulse rate)
 - ➤ Neutrophilic leucocytosis >10.5 × 10⁹/L, or
 - Anaemia.
- Plus, at least one of the following:
 - Dehydration
 - Altered mental status
 - Electrolyte disturbances, or
 - Hypotension.

Investigation

• The most helpful investigation is a plain abdominal X-ray.

- ⇒ Radiological colonic dilatation widest diameter ≥ 6 cm in the transverse colon.
- ⇒ Other radiological findings include:
 - loss of haustral pattern,
 - mucosal oedema and
 - thumbprinting.

Treatment

The treatment of choice for established dilatation is colectomy.

- Treatment includes 3 main goals:
 - reduce colonic distention to prevent perforation (5-fold increase in mortality after free perforation)
 - Rolling techniques (knee-elbow and prone) may be performed to assist in redistribution of colonic gas and decompression
 - Medical treatment:
 - antibiotics to cover the colonic bacterial flora, gram-negative and anaerobic bacteria
 - steroids: either hydrocortisone 100 mg IV every 6 hours or methylprednisolone 60 mg IV every 24 hours is acceptable. The latter has greater relative anti-inflammatory potency and less relative mineralocorticoid potency.
 - cyclosporine may be effective
 - colectomy: Most authors recommend colectomy if persistent dilatation is present or if no improvement is observed on maximal medical therapy after 24-72 hours.
 - 2. correct fluid and electrolyte disturbances
 - fluid replacement, electrolyte repletion, and transfusion should be aggressive.
 - 3. treat toxemia and precipitating factors.
 - Broad-spectrum (IV) antibiotics with coverage equivalent to ampicillin, gentamicin, and metronidazole should be initiated.
 - Possible triggers for TM should be stopped, including:
 - narcotics
 - antidiarrheals
 - anticholinergics

Prognosis

 The mortality rate for non-perforated, acute toxic colitis is about 4%; if perforation occurs, the mortality is approximately 20%.

Gastroenteritis and food poisoning

Radiation enteritis

Overview

- Radiation injury to the rectum and sigmoid colon is commonly seen following treatment of cancers of the cervix, uterus, prostate and bladder.
- It often occurs 9–14 months following radiation exposure and results in a chronically ischaemic intestinal segment that may lead to stricture.
- Symptoms include diarrhoea, obstructed defecation, bleeding, rectal pain or urgency.

Diagnosis

- can be confirmed with colonoscopy, and mucosal features consistent with radiation injury include pallor, friability and telangiectasias.
- Biopsy is not diagnostic but is helpful to exclude other causes.

Treatment

 systemic review of available trials shows promising results for rectal sucralfate and metronidazole combined with topical anti-inflammatory treatment and heater probe.

Gastroenteritis

E. coli is the most common cause of travellers' diarrhoea

Travellers' diarrhoea

- defined as at least 3 loose to watery stools in 24 hours with or without one of more of abdominal cramps, fever, nausea, vomiting or blood in the stool.
- The most common cause is Escherichia coli
- Ciprofloxacin is recommended for first line antibiotic therapy (when needed) before stool culture results are available.

Acute food poisoning

- Sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin.
- typically caused by Staphylococcus aureus, Bacillus cereus or Clostridium perfringens.
- Clostridium perfringens:
 - ⇒ a Gram-positive, rod shaped, anaerobic, spore-forming bacterium.
 - The spores can withstand (بقارع) cooking temperatures, so if food (meat and poultry) is left to stand for a long time, germination of spores can occur, causing food poisoning.
 - ⇒ The CPE (clostridium perfringens enterotoxin) can be detected in food that has been improperly prepared.
 - Clostridium perfringens can also cause gas gangrene, a necrosis of tissues with gas production. The toxin responsible for gas gangrene is called alphatoxin.
- reservoir for this pathogen
 - Vibrio species are most commonly found in seafood (Fish), are commashaped, and prefer alkaline media.
 - ⇒ Improperly **canned foods** are reservoirs for **Clostridium botulinum**. This is an anaerobic gram-positive organism that creates spores. If the can is bulging, it is probably contaminated and should not be eaten.
 - ➡ Honey can be a reservoir for Clostridium botulinum. Newborn babies are at risk for contracting spores from eating honey since their immune systems are poorly developed. This can lead to "floppy baby" syndrome.
 - ⇒ Meats, mayonnaise, custard and other cream-based dishes are food sources commonly associated with <u>Staphylococcus aureus</u> food poisoning.

Diarrhoea

- Osmotic diarrhoea occurs in patients with diabetes who ingest too much sorbitol (a common substitute for glucose in so-called 'diabetic foods'.
- Secretory diarrhoea commonly occurs in response to endotoxin-producing bacteria, (eg cholera or Escherichia coli).

• Chronic radiation enteritis is diagnosed if diarrhoea and abdominal pain persist for 3 or more months following irradiation.

Stereotypical histories

Infection	Typical presentation	
Escherichia coli	Common amongst travellers Watery stools Abdominal cramps and nausea	
Giardiasis	Prolonged, non-bloody diarrhoea	
Cholera	Profuse, watery diarrhoea Severe dehydration resulting in weight loss Not common amongst travellers	
Shigella	Bloody diarrhoea Vomiting and abdominal pain	
Staphylococcus aureus	Severe vomiting Short incubation period	
Campylobacter	commonest cause of bacterial gastroenteritis in the UK A flu-like prodrome is usually followed by crampy abdominal pains (often a prominent feature), 'pseudoappendicitis' (RIF pain), fever and diarrhoea which may be bloody. Treatment: • the most appropriate therapy → IV fluids • most units advocate no antibiotic treatment. • Antibiotic of choice in this infection is erythromycin, though ciprofloxacin and tetracycline may also be appropriate. Complications include Guillain-Barre syndrome	
Salmonella	 After Campylobacter, Salmonella is the most commonly isolated bacterial pathogen when laboratory diagnosis of diarrhea is sought. acute onset of fever, diarrhea, and cramping antibiotic treatment of patients with nontyphoidal salmonellosis may actually prolong, rather than limit, fecal shedding of these organisms. the likely sources are poultry (دواجن) and eggs. 	
Bacillus cereus	Two types of illness are seen vomiting within 6 hours, stereotypically due to rice diarrhoeal illness occurring after 6 hours	
Amoebiasis	Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks	

Incubation period

- 1-6 hrs: Staphylococcus aureus, Bacillus cereus*
- 12-48 hrs: Salmonella, Escherichia coli
- 48-72 hrs: Shigella, Campylobacter

> 7 days: Giardiasis, Amoebiasis

Amoebic dysentery

- Acute amoebic dysentery is managed with:
 - a course of oral metronidazole or tinidazole.
 - 2. followed by a ten day course of diloxanide to eradicate colonisation of the gut.
- · Amoebic liver abscess may appear at any time from eight weeks after infection, and presents with night sweats, anorexia and right upper quadrant pain.
- mortality from amoebiasis is less than 1%.

Biochemical abnormalities in persistent vomiting

- persistent vomiting → ↓↓ gastric hydrochloric acid → hypochloraemia and metabolic **Alkalosis**
- In the early stages the urine has low chloride and high bicarbonate levels in order to compensate for the loss of gastric hydrochloric acid and is appropriately alkaline.
- · With the continued dehydration, sodium is preferentially reabsorbed over the potassium and hydrogen ions which are excreted by the kidneys.
- The urine becomes paradoxically acidic, hypokalaemia develops, and alkalosis leads to lower circulating levels of ionised calcium.

To quickly remember the PH changes associated with GI losses, think:

- With vomiting, both the PH and food come up.
- With diarrhoea, both the PH and food go down.

Giardiasis

Pathogenesis

- Giardiasis is caused by the flagellate protozoan Giardia lamblia.
- Giardia lamblia is capable of causing epidemic or sporadic diarrheal illness.
- It has two morphological forms: cysts and trophozoites. Cysts are the infectious form of the parasite; following cyst ingestion, trophozoites are released in the proximal small intestine. Trophozoites that do not adhere to the small intestine move forward to the large intestine where they revert to the infectious cyst form; these cysts are passed back into the environment in excreted stool.
- Transmission: via the faeco-oral route.
- The incubation period is 1-2 weeks.

Feature

- Often asymptomatic
 - $\Rightarrow \approx 50\%$ clear the infection without symptoms
 - ⇒ ≈ 15% shed cysts asymptomatically (carriers)
- Symptomatic infection ≈ 35%
 - ⇒ lethargy, bloating, abdominal pain
 - ⇒ non-bloody diarrhoea
 - ⇒ malabsorption and acquired lactose intolerance can occur → chronic diarrhoea, steatorrhoea & weight loss

Diagnosis

- stool microscopy
 - initial investigation, but frequently not positive, need 3 samples, 2-3 days apart as cyst and trophozoites are shed intermittently

- Stool antigen tests: immunoassays (eg: ELISA) using antibodies against cyst or trophozoite antigen
 - ⇒ the best test for giardia
 - ⇒ more sensitive and faster than stool microscopy.
- duodenal samples for microscopy: can be obtained by:
 - ⇒ the 'string test' (swallowing a gelatin capsule on a string)
 - ⇒ endoscopy → duodenal aspirates or biopsy.

Treatment

- Antiprotozoal (tinidazole, nitazoxanide or metronidazole)
 - ⇒ Metronidazole has been the first-line; however, a single-dose tinidazole is superior and the best treatment now (shorter course and fewer side effects)
- · For pregnant:
 - ⇒ 1st trimester → paromomycin (Non-absorbable aminoglycoside)
 - ⇒ 2nd & 3rd trimester → either paromomycin or metronidazole

Clostridium perfringens

The food poisoning with Colicky abdominal pain and diarrhoea without vomiting after incubation period between 9-13 hours is typical of *Clostridium perfringens*.

Bacillus cereus

typical case of Bacillus cereus, profuse vomiting occurs one to five hours after eating (rice).

- B.cereus can cause two patterns of disease:
 - 1. classic emetic form:
 - caused by the ingestion of toxin
 - Characterised by nausea and vomiting, similar to Staphylococcus aureus.
 - Rice products are generally the cause of this form.
 - 2. diarrhoeal form:
 - less common
 - Caused by the ingestion of the organism, which releases toxin within the stomach
 - Produce an illness similar to C. perfringens (but the incubation period is classically shorter (1-6 hours) with watery diarrhoea and abdominal cramps.
 - Meats, milk, vegetables and fish have been associated with this form.

Shigella

- · causes bloody diarrhoea, abdominal pain
- severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease
- treat with ciprofloxacin
- Reactive arthritis and Reiter's syndrome can develop following infection with a number of enteric pathogens including Shigella, Salmonella, Campylobacter and Yersinia.

Yersinia enterocolitica

- gram-negative bacillus
- the second most common cause of bacterial gastrointestinal infection in children.
- most frequently associated with enterocolitis, acute diarrhea, terminal ileitis, mesenteric lymphadenitis and **pseudoappendicitis**

- Pseudoappendicitis syndrome is more common in older children and young adults.
- Enterocolitis, the most common presentation of Y enterocolitica, occurs primarily in young children. Most cases are self-limited.
- Y enterocolitica is potentially transmitted by contaminated unpasteurized milk and milk products, raw pork, tofu, meats, oysters, and fish.
- The usual presentation of Y enterocolitica infection includes diarrhea (the most common clinical manifestation of this infection), low-grade fever, and abdominal pain lasting 1-3 weeks. Diarrhea may be bloody in severe cases. Vomiting is present in approximately 15-40% of cases
- Stool culture is the best way to confirm the diagnosis
- Ultrasonography or computed tomography (CT) scanning may be useful in delineating true appendicitis from pseudoappendicitis
- Complications
 - After an incubation period of 4-7 days, infection may result in mucosal ulceration (usually in the terminal ileum and rarely in the ascending colon), necrotic lesions in Peyer patches, and mesenteric lymph node enlargement.
 - In persons with human leukocyte antigen (HLA)—B27, reactive arthritis is not uncommon, possibly because of the molecular similarity between HLA-B27 antigen and Yersinia antigens.
- First-line drugs used against the bacterium include aminoglycosides and trimethoprimsulfamethoxazole (TMP-SMZ). Other effective drugs include third-generation cephalosporins, tetracyclines (not recommended in children < 8 y), and fluoroquinolones (not approved for use in children < 18 y).
- Yersinia pestis is the causative agent of the plague.
- Yersinia bacteria has an ability to survive, and actively proliferate at temperatures as low as 1–4°C (e.g., on food products in a refrigerator).
- Yersinia is one of the causes of reactive arthritis
- Yersinia may be associated with Crohn's disease
 - > Iranian sufferers of Crohn's disease were more likely to have had earlier exposure to refrigerators at home, consistent with its unusual ability to thrive at low temperatures.
- Which bacteria can multiply and produce endotoxin even in refrigerated blood?
 - > Yersinia
 - it is a prominent cause of life-threatening post-transfusion infection.
 - Endotoxins can result in septic shock

Gastrointestinal parasitic infections

Common infections

Organism	Notes
Enterobiasis	 Due to organism Enterobius vermicularis Common cause of pruritus ani Diagnosis usually made by placing scotch tape at the anus, this will trap eggs that can then be viewed microscopically Treatment is with mebendazole
Ancylostoma duodenale	 Hookworms that anchor in proximal small bowel Most infections are asymptomatic although may cause iron deficiency anaemia Larvae may be found in stools left at ambient temperature, otherwise infection is difficult to diagnose

Organism	Notes
	Infection occurs as a result of cutaneous penetration, migrates to lungs, coughed up and then swallowed Treatment is with mebendazole
Ascariasis	 Due to infection with roundworm Ascaris lumbricoides Infections begin in gut following ingestion, then penetrate duodenal wall to migrate to lungs, coughed up and swallowed, cycle begins again Diagnosis is made by identification of worm or eggs within faeces Treatment is with mebendazole
Strongyloidiasis	 Due to infection with Strongyloides stercoralis Rare in west Organism is a nematode living in duodenum of host Initial infection is via skin penetration. They then migrate to lungs and are coughed up and swallowed. Then mature in small bowel are excreted and cycle begins again An auto infective cycle is also recognised where larvae will penetrate colonic wall Individuals may be asymptomatic, although they may also have respiratory disease and skin lesions Diagnosis is usually made by stool microscopy In the UK mebendazole is used for treatment
Cryptosporidium	 Protozoal infection Organisms produce cysts which are excreted and thereby cause new infections Symptoms consist of diarrhoea and cramping abdominal pains. Symptoms are worse in immunosuppressed people Cysts may be identified in stools Treatment is with metronidazole
Giardiasis	 Diarrhoeal infection caused by <i>Giardia lamblia</i>(protozoan) Infections occur as a result of ingestion of cysts Symptoms are usually gastrointestinal with abdominal pain, bloating and passage of soft or loose stools Diagnosis is by serology or stool microscopy First line treatment is with metronidazole

Exotoxins and endotoxins

Definition

 Exotoxins are secreted by bacteria whereas endotoxins are only released following lysis of the cell.

Exotoxins

- Exotoxins are generally released by Gram positive bacteria with the notable exceptions of Vibrio cholerae and some strains of E. coli
- It is possible to classify exotoxins by their primary effects:
 - pyrogenic toxins
 - > enterotoxins
 - > neurotoxins
 - > tissue invasive toxins
 - > miscellaneous toxins

Pyrogenic toxins

- Pyrogenic toxins stimulate the release of endogenous cytokines resulting in fever, rash etc.
- They are super-antigens which bridge the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release.

Organism	Toxin	Notes
Staphylococcus aureus	Toxic shock syndrome (TSST-1 superantigen) toxin	Results in high fever, hypotension, exfoliative rash
Streptococcus pyogenes	Streptococcal pyrogenic exotoxin A & C	Results in scarlet fever

Enterotoxins

- Enterotoxins act on the gastrointestinal tract causing one of two patterns of illness:
 - diarrhoeal illness
 - vomiting illness ('food poisoning')

Organism	Toxin	Notes
Vibrio cholerae	Cholera toxin	Causes activation of adenylate cyclase (via G _s) leading to increases in cAMP levels, which in turn leads to increased chloride secretion and reduced sodium absorption
Shigella dysenteriae	Shiga toxin	Inactivates 60S ribosome → epithelial cell death
Escherichia coli	Heat labile toxin Heat stabile toxin	$ \begin{array}{l} \text{1. Activates adenylate cyclase (via } G_s), increasing cAMP \rightarrow \\ \text{watery diarrhoea} \\ \text{2. Activates guanylate cyclase, increasing cGMP} \rightarrow \text{watery diarrhoea} \\ \end{array} $
Staphylococcus aureus	Staphylococcus aureus enterotoxin	Vomiting and diarrhoeal illness lasting < 24 hours
Bacillus cereus	Cereulide	Potent cytotoxin that destroys mitochondria. Causes a vomiting illness which may present within 4 hours of ingestion

Neurotoxins

 Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing paralysis.

Organism	Toxin	Notes
Clostridium tetani	Tetanospasmin	Blocks the release of the inhibitory neurotransmitters GABA and glycine resulting in continuous motor neuron activity → continuous muscle contraction → lockjaw and respiratory paralysis
Clostridium botulinum	Botulinum toxin	Blocks acetylcholine (ACh) release leading to flaccid paralysis

Tissue invasive toxins

Organism	Toxin	Notes
Clostridium perfringens	α-toxin, a lecithinase	Causes gas gangrene (myonecrosis) and haemolysis
Staphylococcus aureus	Exfoliatin	Staphylococcal scalded skin syndrome

Miscellaneous toxins

Organism	Toxin	Notes
Corynebacterium diphtheriae	Diphtheria toxin	ADP ribosylates elogation factor (EF-2), resulting in inhibition, causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue
Pseudomonas aeruginosa	Exotoxin A	Also inhibits EF-2 by the same mechanism as above
Bacillus anthracis	Oedema factor (EF)	Forms a calmodulin-dependent adenylate cyclase which increases cAMP, impairing the function of neutrophils/macrophages → reduced phagocytosis
Bordetella pertussis	Pertussis exotoxin	Inhibits G_i leading to increases in cAMP levels, impairing the function of neutrophils/macrophages \rightarrow reduced phagocytosis

Endotoxins

 Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as Neisseria meningitidis.

Pseudomembranous colitis (Clostridium difficile)

Pathogen

- Clostridium difficile is a Gram-positive anaerobic rod
- It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.

Causes

- Clostridium difficile develops when the normal gut flora are suppressed by broad-spectrum antibiotics.
 - ⇒ Clindamycin is historically associated with causing *Clostridium difficile* but the aetiology has evolved significantly over the past 10 years.
 - Second and third generation cephalosporins are now the leading cause of Clostridium difficile.
 - ⇒ penicillins and quinolones.

Features

- Symptoms can occur up to 10 weeks following antibiotic therapy.
- Diarrhoea

- ⇒ The commonest symptoms
- ⇒ profuse watery diarrhoea (usually without blood or mucus)
- abdominal pain
- a raised white blood cell count is characteristic
- if severe toxic megacolon may develop

Severity of C. difficile infection

- Mild infection: < 3 episodes of loose stools per day, no ↑WCC.
- Moderate infection: 3 to 5 loose stools per day, WCC <15 × 109 per litre.
- Severe infection:
 - ⇒ WCC >15 × 109 per litre.
 - ⇒ Acutely ↑CRP >50% above baseline,
 - ⇒ Temperature >38.5
 - ⇒ Evidence of severe colitis (abdominal or radiological signs), lactic acidosis
 - ⇒ The <u>number of stools</u> may be a <u>less reliable indicator of severity.</u>
- Life-threatening infection: hypotension, partial or complete ileus, toxic megacolon or CT evidence of severe disease.

Diagnosis

- Clostridium difficile toxin (CDT) in the stool (the most widely used diagnostic tool).
- ELISA tests are specific but not as sensitive.
- Culture is sensitive but often does not differentiate between toxigenic and non-toxigenic
- Sigmoidoscopy may show → multiple white plaques adhered to the gastrointestinal mucosa (pathognomonic).
 - ⇒ 90% of cases can be detected macroscopically by flexible sigmoidoscopy
 - ⇒ mild cases may not be evident macroscopically → microscopic examination of a biopsy sample
 - ⇒ Toxic dilatation should be excluded prior to sigmoidoscopy by doing plain abdominal x-ray.
 - not used routinely
- Plain AXR is useful for diagnosing toxic dilatation
 - ⇒ would be the investigation of choice if there is abdominal distension.
 - **⇒** To exclude toxic dilatation prior to sigmoidoscopy.
 - ⇒ However it does not establish the diagnosis.

Management

Antibiotic treatment for Clostridium difficile (NICE guideline/July 2021)		
Treatment	Antibiotic	
First-line for a first episode of mild, moderate or severe <i>C. difficile</i> infection	Vancomycin:125 mg orally four times a day for 10 days	
Second-line for a first episode of mild, moderate or severe C. difficile infection if vancomycin is ineffective	Fidaxomicin: 200 mg orally twice a day for 10 days	
Third-line: if first- and second-line are ineffective	Vancomycin: Up to 500 mg orally four times a day for 10 days With or without Metronidazole:	

	500 mg intravenously three times a day for 10 days
For relapse : (a further episode of C. difficile infection within 12 weeks of symptom resolution)	Fidaxomicin: 200 mg orally twice a day for 10 days
of C. difficile infection more than	Vancomycin:125 mg orally four times a day for 10 days Or Fidaxomicin: 200 mg orally twice a day for 10 days
	Vancomycin: 500 mg orally four times a day for 10 days With Metronidazole: 500 mg intravenously three times a day for 10 days

- Do not offer antimotility medicines such as loperamide.
- For a recurrent episode (2 or more previous episodes) → Consider a faecal microbiota transplant.

Prognosis

• Mortality is high in elderly patients it may be as high as 10%

Top tips

Cephalosporins, not just clindamycin, are strongly linked to *Clostridium* difficile

The main Clostridium species

- Clostridium botulinum: produce botulinum toxin in food or wounds and can
 cause botulism. This same toxin is known as Botox and is used in cosmetic
 surgery to paralyze facial muscles to reduce the signs of aging; it also has
 numerous other therapeutic uses.
- **Clostridium difficile** can flourish when other gut flora bacteria are killed during antibiotic therapy, leading to pseudomembranous colitis
- Clostridium perfringens causes food poisoning to cellulitis, fasciitis, and gas gangrene.
- Clostridium tetani causes tetanus.
- Clostridium sordellii can cause a fatal infection in exceptionally rare cases after medical abortions

Gastroenteritis (GI)

Causes

- Viral: Most common causes of GI.
 - norovirus is the most common cause of acute gastroenteritis and the second most common cause of hospitalisation for acute gastroenteritis.
 - ⇒ Characteristics of the history that suggest a viral aetiology of acute gastroenteritis include: intermediate incubation period (24–60 h), short infection duration (12–60 h) and high frequency of vomiting.
- Amoebiasis: caused by Entamoeba histolytica (an amoeboid protozoan)
 - ⇒ 10% of the world's population is chronically infected.
 - ⇒ can be asymptomatic, may cause mild diarrhoea

- •
- ⇒ amoebic dysentery → profuse, bloody diarrhoea, stool microscopy may show trophozoites
- ⇒ treatment by metronidazole
- ⇒ Complication → Amoebic liver abscess
 - usually a single mass in the right lobe (may be multiple)
 - features: fever, RUQ pain
 - serology positive in > 90%

Scombrotoxin food poisoning

- Caused by the ingestion of foods that contain high levels of histamine and possibly other vasoactive amines and compounds.
- Histamine and other amines are formed by the growth of certain bacteria and the subsequent action of their decarboxylase enzymes on histidine and other amino acids in food, by spoilage of foods such as;
 - ⇒ fishery products, particularly tuna or mahi mahi.
 - **⇒** dark meat fish such as tuna, mackerel and marlin.
 - ⇒ The most common cause of scombroid poisoning is due to ingestion of spoiled fish following inadequate refrigeration or prolonged time at room temperature. Cooking does not inactivate the toxin/histamines.
- Incubation period
 - **⇒** 10-60 minutes.
- Feature
 - ⇒ The symptoms are due to ingestions of amines, **predominantly histamines**, produced by bacterial decarboxylation of histidine in fish meat.
 - ⇒ Onset is usually 10-30 minutes post-ingestion of the implicated fish but a delayed onset may occur up to two hours.
 - ⇒ Patients with pre-existing conditions such as bronchial asthma, and those taking isoniazid (a histaminase inhibitor) may be more symptomatic.
 - Presented with diarrhoea, flushing, sweating and a hot mouth, minutes after eating
 - ⇒ Urticarial rash, Bronchospasm

Treatment

- · usually self-limiting
- In severe cases, symptoms respond rapidly to antihistamines, for example, chlorpheniramine and intravenous cimetidine by slow intravenous injection over at least five minutes.

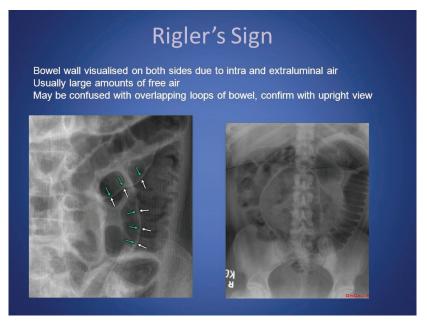
Perforated viscus

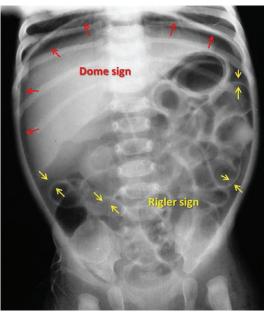
the most appropriate next step in making the diagnosis → abdominal CT scan

Ascitic fluid is normally sterile and any growth of organisms is indicative of infective pathology. Mixed growth suggests a large communication of micro-organisms into the abdominal cavity, which makes perforation the most likely cause.

- Ascitic fluid analysis:
 - ⇒ very bloody ascites
 - ⇒ secondary bacterial peritonitis
 - very inflammatory (very high neutrophil count)
 - exudate (low serum albumin ascites gradient <11 g/L).
 - Gram stain demonstrates multiple bacteria.
- X-ray
 - distended bowel loops (dilated, oedematous)

- > Rigler's sign, which indicates a perforated viscus.
 - also known as the double wall sign, is seen on an X-ray of the abdomen when
 - the air is present on both sides of the intestine, (luminal and peritoneal side of the bowel wall).
- Dome sign
 - Air on the top of the liquid (fluid level)
- pneumatosis coli which are suggestive of ischaemic bowel but not diagnostic of this or perforation.

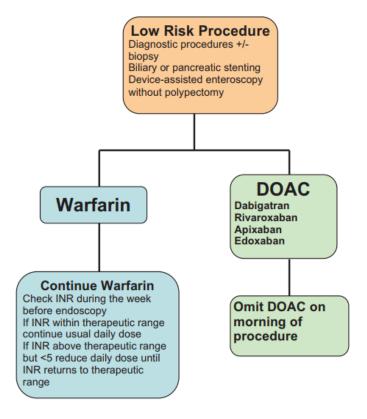




Endoscopy in patients on antiplatelet or anticoagulant therapy

British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines (2016)

- The risk of endoscopy in patients on anti-thrombotics depends on the risks of procedural haemorrhage versus thrombosis due to discontinuation of therapy.
- Where the endoscopic procedure carries a high risk of bleeding and the indication for anticoagulation is low risk for discontinuation then anticoagulation should be discontinued until the INR is <1.5 and restarted post-procedure. Bridging with heparin is not required.
 - Bridging is only recommended if the indication for anticoagulation is high risk for example, mechanical mitral valve, atrial fibrillation (AF) and prosthetic valve, recent venous thromboembolism (VTE) (less than three months), thrombophilia.
 - Low molecular weight heparin (LMWH) is relatively contraindicated in patients with an estimated glomerular filtration rate (eGFR) less than 30 mls/min, these patients may require admission for unfractioned heparin (UFH) infusion.
- Where an endoscopic procedure is associated with a low risk of haemorrhage then the BSG recommends continuation of anticoagulation at the current dosage providing an INR within the last seven days is within the therapeutic range.



High Risk Procedure

Polypectomy ERCP with sphincterotomy Ampullectomy EMR/ESD

Dilation of strictures

Therapy of varices PEG

EUS with FNA

Oesophageal, enteral or colonic stenting

Warfarin

Low Risk Condition

Prosthetic metal heart valve in aortic position Xenograft heart valve AF without valvular disease >3months after VTE Thrombophilia syndromes (liaise

with haematologist)

Stop warfarin 5 days before endoscopy

Check INR prior to procedure to ensure INR<1.5 Restart warfarin evening of procedure with usual daily dose Check INR 1 week later to ensure adequate anticoagulation

High Risk Condition

Prosthetic metal heart valve in mitral position
Prosthetic heart valve and AF AF and mitral stenosis
<3months after VTE

Stop warfarin 5 days before endoscopy

Start LMWH 2 days after stopping warfarin
Give last dose of LMWH ≥ 24 hours before procedure
Restart warfarin evening of procedure with usual daily dose
Continue LMWH until INR adequate

High Risk Procedure

Polypectomy

ERCP with sphincterotomy

Ampullectomy

EMR/ESD

Dilation of strictures

Therapy of varices

PEG

EUS with FNA

Oesophageal, enteral or colonic

stenting

DOAC

Dabigatran Rivaroxaban Apixaban Edoxaban

Take last dose of drug ≥ 48 hours before procedure

For dabigatran with CrCl (eGFR) 30-50ml/min take last dose of drug 72 hours before procedure In any patient with rapidly deteriorating renal function a haematologist should be consulted

Low Risk Procedure Diagnostic procedures +/biopsy Biliary or pancreatic stenting Diagnostic EUS Device-assisted enteroscopy without polypectomy Clopidogrel prasugrel ticagrelor Continue therapy

High Risk Procedure Polypectomy ERCP with sphincterotomy Ampullectomy EMR/ESD Dilation of strictures Therapy of varices EUS with FNA Oesophageal, enteral or colonic stenting clopidogrel prasugrel ticagrelor **High Risk Condition** Low Risk Condition Coronary artery stents Ischaemic heart disease without coronary stent Cerbrovascular disease Peripheral vascular disease Liaise with cardiologist Consider stopping clopidogrel, Stop clopidogrel, prasugrel or ticagrelor 5 days prasugrel or ticagrelor before endoscopy if: >12 months after insertion of 5 days before endoscopy drug-eluting coronary stent Continue aspirin if already >1 month after insertion of bare prescribed metal coronary stent Continue aspirin

Third edition Notes & Notes

For MRCP

Volume 2

By

Dr. Yousif Abdallah Hamad

Updated 2022



Foreword

With the grace of the Almighty Allah, I have introduced the third edition of the popular book, the Notes & Notes for MRCP Part & 2.

The MRCP exam requires a wide range of information, particular thinking, and question directed experience.

This book is directed mainly at those who need comprehensive revision of the topics which commonly appear in the written MRCP exams.

It will be helpful to go through these topics before you start solving the best of the five questions; it is also recommended to go quickly over this book in the last few weeks before the day of your exam.

This new edition contains the new published guidelines.

I hope you will find the maximum benefits from this book to get through MRCP written exams.

To practice the best of five questions we advise you to join the best website for MRCP passonexam.com

For any enquiry or comment, please do not hesitate to contact me.

"The mind is not a vessel to be filled, but a fire to be kindled." – **Plutarch.**

March - 2022
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The 10 Golden Tips for MRCP written exams you will ever need

- 1. For MRCP, do not read hard; read smart.
- 2. Three to six months is usually enough for preparation.
- 3. Practice the best of the five questions as much as possible.
- 4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
- 5. Remember, you are getting ideas and concepts from the questions.
- 6. Time factor in the exam room is the leading killer after poor preparation.
- 7. Manage your time wisely.
- 8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
- Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
- 10. Practice, practice and practice.



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Chapter 5 Cardiology

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Third edition

Notes & Notes

For physician

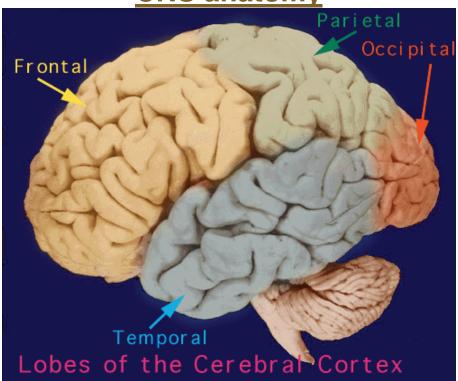
By

Dr. Yousif Abdallah Hamad

Neurology

Updated 2022

CNS anatomy



Localisation of a brain lesion

The following neurological disorders/features may allow localisation of a brain lesion lobes lesions

Lones legiol	Lobes lesions					
Lobe lesion	Features					
Frontal lobes lesions	 Difficulties with task sequencing and executive skills Expressive (Broca's) aphasia: (located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus). Disinhibition Perseveration Anosmia primitive reflexes (positive grasp, pout and palmomental reflexes) Inability to generate a list Changes in personality. 					
Parietal lobes	Sensory inattention (contralateral hemihypesthesia)					
lesions	Apraxia					
	Astereognosis (tactile agnosia)					
	Inferior homonymous quadrantanopia Neglect					
	Mild hemiparesis					
	Parietal ataxia					
	Acalculia (inability to perform mental arithmetic).					
	Gerstmann's syndrome (lesion of dominant parietal): Alexia (inability to read), acalculia, finger agnosia and right-left disorientation					
	 unilateral impairment of optokinetic nystagmus: a nystagmus that occurs in 					
	response to a rotation movement. It is present normally.					
Temporal	Wernicke's aphasia:					
lobes lesions	⇒ this area 'forms' the speech before 'sending it' to Broca's area.					
	⇒ Lesions result in word substitution, neologisms but speech remains fluent					
 superior homonymous quadrantanopia 						
	auditory agnosia					
	prosopagnosia (difficulty recognising faces) Mamory importment					
Occipital	 Memory impairment. homonymous hemianopia (with macula sparing). may present as Anton 					
lobes lesions	syndrome where there is blindness, but the patient is unaware or					
12300 10010110	denies blindness.					
	cortical blindness					
	visual agnosia					
	visual illusions and elementary visual hallucinations.					

Visual- spatial awareness deficit

- Due to the Damage to the right parietal lobe
- Patient unable to navigate around locations, specially places that are new to him, but also familiar locations

Homonymous quadrantanopias

• PITS (Parietal-Inferior, Temporal-Superior)

More specific areas

Area	Associated conditions	
Medial thalamus and mammillary bodies of the hypothalamus	Wernicke and Korsakoff's syndrome	
Subthalamic nucleus of the basal ganglia	Hemiballism	
Striatum (caudate nucleus) of the basal ganglia	Huntington chorea	
Substantia nigra of the basal ganglia	Parkinson's disease	
Amygdala	Kluver-Bucy syndrome: • hypersexuality, • hyperorality (insertion of inappropriate objects in the mouth) • hyperphagia, • visual agnosia increased activation to the amygdala is associated with depression	
Hippocampus pathology	Short term memory impairment (for example, Alzheimer's disease).	
Lateral geniculate nucleus pathology	visual field defect.	
Red nucleus (located in the midbrain).	 Tremor, which is present both at rest and during action (for example, multiple sclerosis tremor). A lesion in this area would cause problems with arm swing and motor co-ordination of the upper limbs, not chorea. 	
Prefrontal cortex damage	disinhibition and problems with social interaction and judgement and has been implicated in schizophrenia. Left prefrontal cortex → Depression	
Anterior hypothalamic nucleus	 Plays a crucial role in thermoregulation and circadian rhythms Situated at the inferior border of the paraventricular nucleus 	

Chorea is caused by damage to the basal ganglia, in particular the caudate nucleus

MRCPUK-part-1-September 2012 exam: (SLE) presents with continuous jerky, irregular movements, which move from one limb to another. Where is the lesion most likely to be?

→ Caudate nucleus

<u>Crossed</u> neurological signs (ipsilateral motor and sensory cranial nerve signs and contralateral hemiplegia) → localise to the <u>brainstem</u> (midbrain, pons or medulla).

- Midbrain → (ipsilateral oculomotor nerve palsy, contralateral hemiplegia)
- Pons → (ipsilateral abducens and facial nerves palsy, contralateral hemiplegia)

Stroke and pupils:

- Midbrain lesions typically cause fixed, midpoint pupils.
- Pontine haemorrhage typically cause bilateral pin point pupils

Lesions at the jugular foramen

- Nasopharyngeal carcinoma is the commonest cause.
- Affected CN → 9,10,11
 - ⇒ CN IX (Glossopharyngeal nerve) & CN X (Vagus nerve) → palatal weakness and swallowing difficulties, Laryngeal muscle paralysis would result in bovine cough and husky voice.
 - ⇒ CN XI (Accessory nerve) → shoulder and sternocleidomastoid weakness

Cerebellar lesions

Cerebellar lesion localization:

- Lesions to the vermis results in → truncal ataxia and nystagmus.
- Cerebellar lesions cause neurological deficits on the ipsilateral side
- Lesions to the cerebellar hemispheres results in → ipsilateral dysmetria, dysdiadochokinesis, ipsilateral limb ataxia and fast-beat nystagmus towards the lesion.

A history of vertigo, nystagmus, Slurred speech, intention tremor and past pointing, as well as ataxia, suggest the cerebellum as the site of injury.

Oppenheim's sign is seen when scratching of the inner side of leg leads to extension of the toes. It is a sign of cerebral irritation

Cerebellum lesions: Charcot's neurological triad: scanning speech, nystagmus, and intention tremors

Transient ischaemic attack (TIA)

Definition

Temporary cerebral ischemia that results in brief neurologic deficits lasting < 24 hours

Investigations (NICE guidelines, Last updated: March 2019)

- MRI is the first choice, identifies ischemia earlier than CT, determine the territory of ischaemia, and detect alternative pathologies.
- Do not offer CT brain unless there is clinical suspicion of an alternative diagnosis.
- Duplex ultrasound for carotid stenosis
 - ⇒ urgent for possible carotid endarterectomy.
 - the most appropriate next step if bruits in the neck are heard upon auscultation.
 - ⇒ If ultrasound is not available, a CTA or MRA may be used.

Treatment

- Immediate therapy (after initial assessment)
 - ⇒ **Aspirin** 300 mg immediately unless contraindicated
 - ⇒ To be seen within 24 hours of onset of symptoms for specialist assessment
 - ⇒ **Do not use scoring systems, such as ABCD2**, to assess risk of subsequent stroke or to inform urgency of referral.
- Secondary prevention (introduced as soon as the diagnosis is confirmed)
 - ⇒ Clopidogrel 300 mg loading dose followed by 75 mg daily.
 - aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel
 - ⇒ **High intensity** (e.g. atorvastatin 20-80 mg daily)
 - started immediately (as per Royal College guideline 2016)
 - Immediate initiation of statin is not recommended as per (NICE guideline 2019)
 - ⇒ Carotid endarterectomy: for people with non-disabling stroke or TIA:
 - carotid stenosis of 50 to 99%:
 - referred urgently for carotid endarterectomy
 - medical treatment (BP control, antiplatelets, Statin, lifestyle advice).
 - carotid stenosis of less than 50%:
 - No surgery
 - Medical treatment (BP control, antiplatelets, Statin, lifestyle advice).
 - ⇒ Control BP: antihypertensive
 - ⇒ If associated AF → Anticoagulation

Top Tips

Antiplatelets TIA: clopidogrel

ischaemic stroke: clopidogrel

Brain imaging for TIA and stroke

- MRI brain with diffusion-weighted imaging is the preferred modality in patients with suspected TIA.
- Non-contrast cranial CT (gold standard and most important initial imaging in stroke): detects acute hemorrhage but cannot reliably identify early ischemia

Ischaemic stroke: Overview

Definition

 Stroke is an acute neurological deficit lasting more than 24 hours due to occlusion or critical stenosis of a cerebral artery.

Epidemiology

• Ischemic stroke (~ 85%)

Risk factors

• older age, hypertension, smoking, diabetes mellitus, dyslipidaemia, atrial fibrillation, sickle cell disease, and history of TIA or stroke.

Mechanisms

- Thrombotic strokes (most common)
 - Atherosclerosis of the <u>extracranial vessels</u> (carotid atheroma) is the most common cause
- Embolic strokes
 - ⇒ Cardiac emboli e.g. Atrial fibrillation
 - Paradoxical embolisation: For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart.
 - Causes
 - patent foramen ovale : present in 20% of the population.
 Transoesophageal echocardiography (TOE) is the investigation of choice for diagnosis
 - atrial septal defect a much less common cause

Assessment

- ROSIER score (Recognition Of Stroke In the Emergency Room).
 - It is validated tool recommended by the Royal College of Physicians. useful for medical professionals.
 - ⇒ Exclude hypoglycaemia first, then assess the following:

Assessment	Scoring
Loss of consciousness or syncope	- 1 point
Seizure activity	- 1 point
New, acute onset of:	
asymmetric facial weakness	+ 1 point
asymmetric arm weakness	+ 1 point
asymmetric leg weakness	+ 1 point
speech disturbance	+ 1 point
visual field defect	+ 1 point

⇒ stroke is likely if > 0

Imaging

- CT without contrast for acute presentation (the best initial test) → to rule out hemorrhage
- MRI: if the CT is negative → Diffusion weighted imaging (DWI) MRI is the most sensitive and specific imaging modality for diagnosing acute ischaemic stroke.
- · Duplex ultrasound for carotid stenosis

Diagnostic evaluation

- Glucose: the only lab test which should be done before thrombolysis
- ECG: to look for cardiogenic thrombus (Atrial fibrillation)
- If an embolic stroke is suspected → Echocardiography
- Thrombophilia screening: if patient is < 50 years old and/or has a history of thrombosis

Only glucose test and CT head are required before thrombolytic therapy. Do not delay treatment to complete the diagnostic evaluation.

Management

- Exclude hypoglycaemia because it is a stroke mimic
- Admission to a stroke unit → improve the overall prognosis.
- presentation within 4.5 hours AND thrombolysis not contraindicated → thrombolysis with iv alteplase
- presentation after 4.5 hours OR thrombolysis contraindicated → Supportive care
- Deep vein thrombosis prophylaxis with subcutaneous heparin or low molecular weight heparin
 - ⇒ Pulmonary embolism from DVT is the most common cause of early death in patients with acute stroke.

Vitamin D has a role as a neuroprotective agent towards large artery atherosclerosis. Many patients with ischemic stroke have vitamin D deficiency.

Stroke: Clinical features Affected cerebral vessels and associated features

Site of the lesion	Associated effects		
Anterior cerebral artery (ACA)	Contralateral weakness and sensory loss more marked in the lower limbs than in upper limbs Urinary incontinence Dysarthria		
Middle cerebral artery	 Contralateral weakness and sensory loss more marked in the upper limbs than in lower limbs Contralateral homonymous hemianopia Aphasia if in dominant hemisphere (usually left MCA territory (global aphasia) Hemineglect if in nondominant hemisphere (usually right MCA territory Gaze deviates toward the side of infarction 		
Posterior cerebral artery	 Contralateral homonymous hemianopia with macular sparing Visual agnosia Cortical blindness Visual hallucinations 		
Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain) Or branches of the basilar artery	Ipsilateral CN III palsy Contralateral weakness		
Posterior inferior cerebellar artery (PICA)(lateral medullary syndrome, Wallenberg syndrome) lesion to dorsolateral medulla	 Ipsilateral: facial pain and temperature loss Contralateral: limb/torso pain and temperature loss. Ataxia, nystagmus 		
Anterior inferior cerebellar artery (lateral pontine syndrome)	Symptoms are similar to Wallenberg's (see above), but: Ipsilateral : facial paralysis and deafness		
Retinal/ophthalmic artery	Amaurosis fugax		
Basilar artery	'Locked-in' syndrome		

Lateral medullary syndrome (Wallenberg's syndrome)

Lateral medullary syndrome:

- Caused by → PICA lesion
- Characterised by :
 - ⇒ Ipsilateral cerebellar signs (Ataxia, Nystagmus) & Horner syndrome (ptosis, miosis, and anhidrosis).
 - ⇒ Contralateral trunk and limbs sensory loss

Pathophysiology

- Ischemic occlusion of the Posterior Inferior Cerebellar Artery (PICA) → Iesion to dorsolateral medulla
- May caused by dissection or thrombosis of the vertebral artery, which gives rise to the
 posterior inferior cerebellar artery (PICA)
- PICA is the largest branch of the vertebral artery and is the most common territory involved in cerebellar infarction.
- The PICA supplies blood to structures of the lateral medulla (vestibular nuclei, spinal cord tracts) and the inferior cerebellar peduncle.

Features

- Vertigo, nausea and truncal ataxia are the most common presenting features and due to vestibular or cerebellar damage.
- Hoarseness (or dysphagia, if present) is fairly specific for lateral medullary syndrome because it points to a lesion of the nucleus ambiguous (cranial nerves IX, X, XI).
- Damage to the spinal **trigeminal nucleus** can result in **loss of pain and temperature** sensation in the ipsilateral face.
- Damage to the **lateral spinothalamic tract** can result in loss of contralateral pain and temperature sensation below the neck.
- Damage to the descending sympathetic fibers that also course through the lateral medulla would result in an ipsilateral Horner syndrome of ptosis, miosis, and anhidrosis.
- Ataxia is probably due to infarction of the ipsilateral inferior cerebellar peduncle.
- Pyramidal tract findings (weakness) are **typically absent** in lateral medullary lesions.

1	psilateral	Contralateral
•	Cerebellar signs (Ataxia, dysmetria, dysdiadochokinesia, nystagmus) Horner syndrome Loss of pain and temperature in the	Loss of pain and temperature in the trunk and limbs
	face (due to 5 th CN nucleus damage)	

Diagnosis: MRI is the imaging investigation of choice for posterior fossa lesions.

Lateral pontine syndrome VS Lateral medullary syndrome

	Lateral pontine syndrome	Lateral medullary syndrome
Aetiology	Anterior inferior cerebellar artery (AICA)	posterior inferior cerebellar artery (PICA)
Differences	 Facial nucleus and facial nerve involvement leads to: Ipsilateral paralysis of the upper and lower face (lower motor neuron lesion). Ipsilateral loss of lacrimation and reduced salivation. Ipsilateral loss of taste from the anterior two-thirds of the tongue. Hyperacusis. 	Nucleus ambiguous involvement leads to: Dysphagia, dysarthria, dysphonia
Similarities	Ipsilateral Horner's syndrome. Why? Descending hypothalamic tracts affected. Contralateral loss of pain and temperature. Why? Lateral spinothalamic tract affected. Ipsilateral cerebellar ataxia. Why? Cerebellar peduncles affected. Inferior cerebellar peduncle in medullary and middle cerebellar peduncle in pons. Nausea, nystagmus, vertigo, vomiting. Why? Vestibular nuclei involved. Ipsilateral loss of pain and temperature sensation from the face (facial hemianesthesia). Why? Spinal trigeminal nucleus and tract involved. Ipsilateral hearing loss.	

Pontine syndromes

Locked-in syndrome

- Pathophysiology
 - ⇒ The locked-in syndrome is caused by destructive bilateral brainstem lesions affecting the corticospinal, corticopontine, and corticobulbar tracts.
 - ⇒ The most common cause is ischemic **infarction of the ventral pons**.
- Features
 - □ Quadriplegia and inability to speak or swallow with retained consciousness and eyes movement

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⇒ Because the supranuclear ocular motor pathways are spared, patients can move their eyes and blink.

Ventral pontine syndrome

- Millard-Gubler syndrome (MGS), also known as facial abducens hemiplegia syndrome is
 one of the classical crossed brainstem syndromes characterized by a unilateral lesion of
 basal portion of the caudal *pons* involving fascicles of abducens (VI) and the facial (VII)
 cranial nerve, and the pyramidal tract fibers
- Classical Raymond syndrome also has the same components as Millard-Gubler syndrome, but there is ipsilateral sixth nerve palsy along with contralateral facial paresis and hemiplegia.

Components of Millard-Gubler syndrome (MGS)

- **1.** Ipsilateral weakness of the eye on abduction (VI nerve)
- 2. Ipsilateral facial muscle weakness (VII nerve)
- Contralateral hemiparesis or hemiplegia of upper and lower extremities (pyramidal tract involvement)

Inferior medial pontine syndrome

 Inferior medial pontine syndrome, also known as Foville syndrome, is one of the brainstem stroke syndromes occurring when there is infarction of the medial inferior aspect of the pons due to occlusion of the paramedian branches of the basilar artery.

Features

- ⇒ corticospinal tract: **contralateral** hemiplegia/hemiparesis
- ⇒ medial lemniscus: **contralateral** loss of proprioception and vibration
- ⇒ middle cerebellar peduncle: ipsilateral ataxia
- ⇒ facial nerve (CN VII) nucleus: ipsilateral facial weakness
- ⇒ abducens nerve (CN VI) nucleus: lateral gaze paralysis and diplopia

Weber's syndrome

Weber syndrome

- ipsilateral III palsy
- contralateral weakness

Overview

- **Weber syndrome** is a <u>midbrain</u> stroke syndrome that involves the cerebral peduncle and the ipsilateral fascicles of the oculomotor nerve
- caused by midbrain infarction as a result of occlusion of the paramedian branches of the posterior cerebral artery or of <u>basilar</u> bifurcation perforating arteries.

Features

- Ipsilateral III palsy
- Contralateral weakness

Parinaud syndrome (Dorsal midbrain syndrome)

Pathophysiology

- Results from dorsal midbrain lesion
- Affected vessel: Branches of the posterior cerebral artery. Often result from compression, e.g., by tumor of the pineal gland → compresses the vertical gaze center at the rostral interstitial nucleus of medial longitudinal fasciculus → vertical gaze palsy

Feature

- Vertical gaze palsy (inability to move the eyes up). Downward gaze is usually preserved
- Eyelid retraction (Collier sign): development of unilateral or bilateral lid retraction due to a midbrain lesion of the superior colliculi and the medial longitudinal fasciculus.
- Pupillary light-near dissociation (pseudo-Argyll Robertson pupils)
- Convergence-retraction nystagmus

Labyrinthine infarction

<u>Sudden</u>-onset unilateral hearing loss → consider <u>Labyrinthine infarction</u> typically due to anterior cerebellar artery dissection after minor head trauma

Anatomy

The blood supply to the inner ear flows through only 1 main blood vessel, the internal
auditory artery (or labyrinthine artery), which typically originates from the anterior inferior
cerebellar artery.

Features

- almost always present with acute prolonged vertigo and vestibular dysfunction
- sudden-onset unilateral hearing loss.

Differential diagnosis

 Unlike viral labyrinthine dysfunction, the most common pattern of dysfunction with labyrinthine infarction includes a combined loss of auditory and vestibular function.

Posterior communicating artery aneurysm (PCA)

Posterior communicating artery aneurysm will cause → compression of the third nerve, and therefore → isolated **ipsilateral painful** third nerve palsy

- Pupillary involvement (pupil dilation) from compression of the parasympathetic fibres that run on the outside of the third nerve
- Other features of a third nerve palsy include ptosis, and a 'down and out' eye.
- Cerebral aneurysms may be associated with polycystic kidney disease.

Features

- Pupillary dilatation, Ophthalmoplegia, and Ptosis.
- other features suggestive of subarachnoid blood (headache, nuchal rigidity and photophobia).

Investigation

Urgent CT angiogram of the cerebral vessels is required for diagnosis.

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- Conventional angiography: the definitive procedure for the detection and characterisation of cerebral aneurysms.
- **Digital subtraction angiography:** may be helpful in identifying an acutely ruptured aneurysm.

Differential diagnosis

 Features distinguishing PCA from a cavernous sinus thrombosis are absence of sinusitis or a midface infection, which are common, absence of fever or additional cranial nerve abnormalities.

The differential diagnoses in a patient presenting with headaches and painful diplopia are:

- posterior communicating aneurysm (PCA)
- · Ophthalmoplegic migraine
- Pituitary adenoma
- · Cavernous sinus thrombosis, or
- medical mononeuritis.

Ischaemic Stroke management

Initial management

• Aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded for the initial two weeks.

Reperfusion therapy for acute ischemic stroke

- Thrombolysis by Alteplase (recombinant tissue plasminogen activator or tPA) are commonly used
 - - Alteplase → bind to fibrin in a thrombus (clot) → convert entrapped plasminogen to plasmin → plasmin breaks up the thrombus → fibrinolysis
 - ⇒ **Criteria**: Ischemic stroke with the onset of symptoms <4.5 hours
 - ⇒ Written consent is not required to administer alteplase
 - ⇒ Absolute contraindications
 - Ischemic stroke, head trauma or surgery in the previous three months
 - Previous intracranial hemorrhage
 - Intracranial neoplasm
 - Gastrointestinal malignancy or hemorrhage in the previous 21 days
 - Cerebral hemorrhage
 - Persistent High BP (systolic ≥185 mmHg or diastolic ≥110 mmHg)
 - Haematological bleeding disorders
 - ⇒ Bleeding risk: 1 %.
- Mechanical thrombectomy: a device that can remove a clot
 - ⇒ patients should undergo the procedure within 6 hours of symptom onset.
 - ⇒ Indications
 - large vessel occlusion (usually in addition to IV thrombolytic therapy) proximal
 MCA or distal internal carotid artery or basilar artery occlusion.
 - Patients who are ineligible for IV thrombolysis who present within the appropriate time-frame with large vessel occlusion.

Surgical treatment → decompressive hemicraniectomy

- Indications: Patient with middle cerebral artery infarction who meet all of the criteria below:
 - 1. Age ≤ 60 years
 - Clinical deficits suggestive of infarction in the territory of the middle cerebral artery, with a score on the National Institutes of Health Stroke Scale (NIHSS) of above 15.
 - 3. Decrease in the level of consciousness to give a **score of 1 or more** on item 1a of the **NIHSS.**
 - 4. Signs on CT of an infarct of at least 50% of the middle cerebral artery territory

For individuals aged up to 60 years who suffer an acute MCA territory ischaemic stroke complicated by massive cerebral oedema, surgical decompression by hemicraniectomy should be offered within 48 hours of stroke onset.

Secondary prevention

- Clopidogrel is now recommended by NICE
 - ⇒ if clopidogrel is not tolerated → Aspirin + dipyridamole lifelong
 - Anticoagulation treatment for other comorbidities (e.g. atrial fibrillation):
 - ⇒ Should not be started until brain imaging has excluded haemorrhage, usually **after 14 days** from the onset of an **ischaemic stroke**.
 - ⇒ ischaemic stroke + atrial fibrillation → aspirin 300 mg for the first 2 weeks before considering anticoagulation treatment.
 - □ cerebral infarction in patient with prosthetic valves and who are at significant risk of haemorrhagic transformation →anticoagulation treatment should be stopped for 1 week and aspirin 300 mg substituted.
 - ⇒ ischaemic stroke and symptomatic proximal DVT or PE → should receive
 anticoagulation treatment in preference to treatment with aspirin
 - ⇒ haemorrhagic stroke and symptomatic DVT or PE → prevent further PE using either anticoagulation or a caval filter.
 - ⇒ Prevention of thromboembolic event in stroke patient:
 - Patients admitted with stroke are very likely to be at high risk of developing a thromboembolic event due to reduced mobility.
 - NICE advises that patients admitted within three days of an acute stroke should have intermittent pneumatic compression considered. This should be provided for 30 days or until the patient is mobile or discharged.
- Statin
 - All patients who are diagnosed with stroke or TIA should be commenced on statin therapy irrespective of the cholesterol level.
 - ⇒ If the patient is unable to tolerate a statin (Stroke guidelines by Royal college of physicians 2016):
 - try alternative methods to improve the tolerability of a statin such as a reduced dose, alternate day dosing or a lower-intensity statin
 - Do not use fibrates, ezetimibe, bile acid sequestrants, nicotinic acid or omega-3 fatty acids for cholesterol-lowering after stroke
- Management of hyperglycaemia
 - ⇒ The European Stroke Initiative guidelines recommend treatment for glucose >180 mg/dL (>10 mmol/L)

- ⇒ The Joint British Diabetes Society 2012 guidelines recommend a target BM of between 6 and 12 mmol/l for hyperglycaemic patients on NG feed with insulin to be started when BM over 12 mmol/l.
- ⇒ The insulin regime of choice is a biphasic insulin with a mixture of intermediate and short acting insulin twice daily
- Management of blood pressure in acute stroke
 - ⇒ If thrombolytic therapy is indicated → BP should be maintained ≤185/110 mmHg, before thrombolytic therapy (Labetalol, Nicardipine or Clevidipine are used as first line)
 - ⇒ If thrombolytic therapy is not indicated:
 - treat high BP only if the systolic BP >220 mmHg or diastolic BP >120 mmHg
 - cautious lowering of BP by approximately 15% during the first 24 hours.

Top Tips

Time window for:

- Thrombolysis (IV Alteplase): < 4.5 hours
- Mechanical thrombectomy: < 24 hours

Hypertension should not be treated in the initial period following a stroke unless complications develops

Stroke thrombolysis - only consider if less than 4.5 hours and haemorrhage excluded

Haemorrhagic stroke

Spontaneous Intracerebral haemorrhage (ICH)

Epidemiology

- Hemorrhagic stroke (~ 15%)
 - ⇒ The putamen is the commonest site for hypertensive intracerebral haemorrhage

Risk factors

Hypertension (the most common risk factor), older age, haemophilia, cerebral amyloid
angiopathy, anticoagulation, use of illicit sympathomimetic drugs, history of heavy alcohol,
and vascular malformations.

Classification by location

- Lobar ICH
 - ⇒ commonly due to **cerebral amyloid angiopathy** (CAA).
 - Amyloid deposition in small-sized to medium-sized cortical perforators may lead to the rupture of these vessels.
- Non-lobar ICH

commonly due to long-standing high blood pressure resulting in lipohyalinosis of small perforating arteries of the basal ganglia, thalamus, pons and cerebellum, leading to deep haemorrhages, often with extension into the ventricles.

Feature

- ICH should be suspected in any patient with severe headache, vomiting, elevated systolic blood pressures or decreased level of consciousness.
- Fever is common
 - ⇒ Sustained fever after ICH is an independent prognostic factor for worse outcome.

Pontine haemorrhage commonly presents with reduced GCS, paralysis and bilateral pin point pupils

Diagnosis

Non-contrast head CT is highly sensitive and specific

Treatment

- Stabilisation of airway, breathing and circulation (ABCs). Intubation for airway protection is indicated in patient with GCS ≤8 or significant respiratory distress.
- Intensive lowering of systolic blood pressure to <140 mm Hg
 - Intravenous calcium channel blockers (eg, nicardipine) and β-blockers (eg, labetalol) are the treatment of choice for early BP reduction, given their short half-life and ease of titration.
 - ⇒ **During acute phase**, patients may have **resistant HTN due to sympathetic surge**. A few weeks later, they may require fewer medications and be at risk of hypotension unless the doses of medications are adjusted promptly
- **Hyperosmolar therapy** (Mannitol or hypertonic saline)
 - ⇒ **Peri-haematoma oedema** (PHE) develops within the first few days after ICH and may cause elevated ICP, mass effect, midline shift and brain herniation
 - ⇒ **asymptomatic PHE** require **no specific treatment** except maintaining a normal sodium goal → **Observe**
 - \Rightarrow symptomatic cerebral oedema and elevated ICP \rightarrow mannitol and hypertonic saline (HTS) are the first-line
 - Mannitol is an osmotic diuretic. It increases water excretion by the kidneys and reduces cerebral oedema and ICP.
 - HTS increases plasma osmolarity and the flow of excess water from cerebral tissue to the blood via the osmotic gradient.
 - hypertonic saline is slightly more effective than mannitol for the treatment of elevated ICP.
 - ⇒ keep serum sodium level at 140–150 mEq/L for 7–10 days to minimise oedema expansion and mass effect.

Reversal of coagulopathies

intracerebral haemorrhage in association with	reversed with
Vitamin K antagonist (warfarin)	combination of prothrombin complex concentrates (PCC) and intravenous vitamin K. If not PCC not available → fresh frozen plasma (FFP).
Dabigatran	Idarucizumab
Factor Xa inhibitors (eg, rivaroxaban, apixaban and edoxaban) OR other Direct thrombin inhibitors apart from Dabigatran.	Prothrombin complex concentrate (PCC)
Low-molecular-weight heparin	Protamine
Thrombolytic (eg, recombinant tissue plasminogen activator (rtPA))	1 st line → cryoprecipitate administration. 2 nd line (If cryoprecipitate is contraindicated or unavailable) → tranexamic acid (anti- fibrinolytic agent)

- Neurosurgery: Patient with a decreased level of consciousness from intraventricular haemorrhage with hydrocephalus, mass effect or brainstem herniation should receive ventriculostomy.
- Venous thromboembolism (VTE) prophylaxis with intermittent pneumatic compression (IPC) devices

Top tips

Haemorrhage associated with dabigatran → Idarucizumab

Cerebral venous thrombosis (CVT)

Patients with a hypercoagulable state (e.g. pregnancy) and papilloedema with neurological signs should be investigated for cerebral venous thrombosis.

Basics

- Structure: reflections in dura matter where meningeal and periosteal layers split
- Function: return blood from cerebral veins to internal jugular vein
- veins contain NO valves

Epidemiology

more common in young women. Sex: ♀ > ♂, 3:1. Age of onset: ≤ 40 years

Types

- Superior sagittal sinus thrombosis (SSST) is the most common type of dural venous sinus thrombosis
- Cavernous sinus thrombosis (CST) \rightarrow 3rd, 4th and ophthalmic (V1) and maxillary (V2) divisions of the 5th cranial nerve affected

- Superior orbital fissure syndrome: similar to the cavernous sinus syndrome except for the presence of proptosis.
- Lateral sinus thrombosis → 6th and 7th cranial nerve palsies

Risk factors

- Local infection: e.g. Sinusitis, furuncle (Staphylococcus aureus is the most common)
- · Diabetes mellitus
- Hypercoagulable states: pregnancy, post-partum period
- Malignancy
- Clotting disorders (e.g., factor V Leiden, protein C and S deficiencies, antiphospholipid syndrome)
- Polycythemia
- Medications: Oral contraceptive pill, Corticosteroids

Features

- Raised intracranial pressure (ICP)
 - ⇒ Headache: the most common presenting symptom
 - ⇒ Nausea & vomiting: Vomiting in the morning is characteristic of raised ICP as it follows a period of lying flat.
 - ⇒ visual disturbance.
 - ⇒ Papilloedema.
- · Peri-orbital oedema
 - ⇒ may be the earliest physical finding
 - ⇒ Chemosis, oedema and cyanosis of the upper face occur due to obstruction of the ophthalmic vein.
 - ⇒ Eye swelling begins as a unilateral process and spreads to the other eye within 24-48 hours via the intercavernous sinuses. This is pathognomonic for cavernous sinus thrombosis (CST).
- Cranial nerve symptoms (e.g. Ophthalmoplegia):
 - ⇒ CN VI → Lateral gaze palsy (patient cannot abduct eye) is usually seen first.
 - ⇒ CN III → Ptosis, mydriasis, and eye muscle weakness
 - ⇒ CN V → Hyperaesthesia of upper face and eye pain
- **Seizures** (focal or generalized)

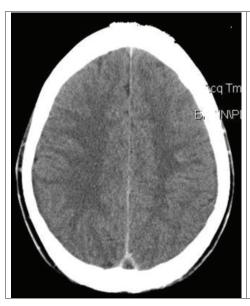
Investigations

- . If CVT is suspected, D-dimer levels and imaging studies are first steps of diagnosis
- Contrast-enhanced CT scan is the test of choice to confirm the diagnosis
 - ⇒ shows a **filling defect** in a vein or sinus, the <u>reverse delta sign</u> (that is, empty triangle sign).
 - ⇒ On contrast CT → empty delta sign (is a specific to the superior sagittal sinus)
 - ⇒ Plain CT/MRI help detect only edema and/or infarcts, but the thrombus itself can be visualized by means of venography.
- Evaluation for possible causes (e.g. CBC, CRP, Thrombophilia screen, antibody studies)

Treatment

- Anticoagulants (full-dose heparin then warfarin).
- Dexamethasone can be used to reduce cerebral oedema.
- Surgical therapy (e.g. Shunt or clot removal) indications:

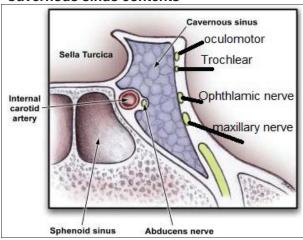
- ⇒ Progressive neurologic worsening (despite adequate anticoagulation)
- ⇒ Acute rise in intracranial pressure
- ⇒ Impending herniation



Empty delta sign indicating a superior sagittal sinus thrombosis

- CT with contrast demonstrating a superior sagittal sinus thrombosis showing the typical empty delta sign.
- Look at the 'bottom' of the scan for the triangular shaped dural sinus.
- This should normally be white due to it being filled with contrast.
- The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx.
- This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

Cavernous sinus contents



Structures passes through the cavernous sinus:

- Internal carotid artery
- Cranial nerves:
 - ⇒ third, fourth, and sixth cranial nerves
 - Ophthalmic (V1) and maxillary (V2) divisions of the fifth cranial nerve

The mandibular branch of the trigeminal nerve (V3) does not travel in the cavernous sinus and would therefore not be affected. (NO lower face symptoms)

Which group of nerves run through the cavernous sinus?
→ III, IV, (V-1, V-2), and VI

MRCPUK-part-1-September 2012: Left-sided eye pain & diplopia for the past 2 days + 6th & 3rd cranial nerve palsy on the left side + hyperaesthesia of the upper face on the left side. Where is the likely lesion?

→ Cavernous sinus

Cervical vascular dissection (Carotid and Vertebral artery dissection)

Stroke provoked by minimal trauma (e.g. exercise) is likely due to Cervical vascular dissection until proven otherwise

Triad of carotid dissection:

- 1. unilateral (ipsilateral) headache
- 2. ipsilateral Horner's syndrome and
- 3. contralateral hemisphere signs (aphasia, neglect, visual disturbance,

Overview

- · Important causes of stroke in young patients
- The two commonest causes of **young onset stroke** (less than 40 years) are
 - 1. Cardio-embolism and
 - 2. Cervical artery dissection.
- Dissection of the internal carotid artery can occur intracranially or extracranially
 - ⇒ Extracranially is more common. 75% of carotid dissections affect the internal carotid artery (that is, extracranially)

Mechanism of ischaemia

- Emboli from the site of the dissection (85-95%) of cases → ischaemic symptoms
- vessel narrowing (5-15%): subintimal tears → intramural haematomas → protrude inward and narrow the vessel lumen.

Causes

- Mechanical forces (eg, trauma, blunt injury, and stretching)
- Arteriopathies (eg, Ehlers-Danlos syndrome, Marfan syndrome and other connective tissue disorders)

Features

- <u>Pain</u> (Headache, neck or facial pain): is the initial common symptom, ipsilateral to the dissected artery.
- Ischaemic neurological features (transient or completed strokes): Sudden-onset
- Partial <u>Horner</u> syndrome (<u>Ptosis</u> with <u>miosis</u>)
 - ⇒ usually **painful** when caused by internal carotid artery dissections
 - The term partial Horner syndrome is used for the oculosympathetic palsy because anhydrosis is absent. Because the sympathetic fibers innervating the facial sweat glands are anatomically located on the external rather than the internal carotid artery

Diagnosis

- Plain CT head <u>first</u> to exclude haemorrhagic stroke
- Computed tomography angiography (CTA) head and neck
 - ⇒ the diagnostic modality of choice.

Carotid dissection

- Younger age group <50 years.
- Neck pain.
- Associated with vigorous exercise or event that sustains severe neck movement (e.g., roller coaster ride, motor vehicle accident).
- May have Horner's syndrome or history of genetic collagen abnormality.

Vertebral artery dissection:

The typical presentation of vertebral artery dissection is a **young person** (average age 40 years) with severe **occipital headache** and **neck pain** following a **recent head or neck injury**. The trauma is often trivial but is usually associated with some form of cervical distortion.

Vertebral artery dissection presents with:

- Brainstem Stroke or transient ischaemic attack
- Pain in the ipsilateral neck, face or head.
- Commonly occurring in young people following a recent head or neck injury.

Carotid artery stenosis

Carotid endarterectomy for stroke or TIA in the carotid territory only indicated if:

- 1. ≥50% ipsilateral carotid stenosis
- 2. The patient not severely disabled
- Carotid artery stenosis causes 10% to 15% of all ischaemic strokes.
- the annual risk of stroke in patients with asymptomatic carotid disease is between 1% and 2%

Pathophysiology

- Atherosclerotic plague in the cervical carotid artery is the most common cause.
- Plaque disruption and athero-embolisation into the intracranial circulation is the most common mechanism for stroke.
- The most common site of carotid Atherosclerosis:
 - ⇒ usually at the fork where the common carotid artery divides into the internal and external carotid artery.

Features

- The majority are asymptomatic.
- TIA or stroke
 - ⇒ Plaques rupture → embolism to intracranial arteries → (TIA or stroke) or embolism to retinal arteries → (amaurosis fugax or retinal strokes).
- Cervical bruit

Diagnosis

- Duplex ultrasonography is the preferred initial mode of diagnosis and screening.
 - ⇒ sensitivity of 99%, specificity of 86%
 - \Rightarrow If the stenosis is less than 50% \rightarrow no further imaging is needed.

- \Rightarrow If the stenosis > 50% \rightarrow CTA or MRA for more detailed plaque characterization.
- CT or Magnetic resonance <u>angiography</u> (CTA or MRA) helps to define the anatomy if intervention is indicated.

Management

- Initial management → Antiplatelet therapy, Statin and risk factor modification.
- Carotid revascularization → Endarterectomy
 - ⇒ Indications:
 - Significant stenosis:
 - Carotid stenosis > 70% according ECST criteria (European Carotid Surgery Trial' Collaborative Group) or > 50% according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.
 - TIA or resolving stroke (The patient not severely disabled):
 - The benefit of endarterectomy is prevention of future stroke, with dense strokes, if there is no recovery, the benefits are greatly reduced due to end-organ damage.
 - Asymptomatic carotid stenosis ≥ 70%: 1st line → antiplatelet therapy and cardiovascular risk reduction. the best course of action? → Discharge and outpatient follow up
 - ⇒ Contraindications:
 - 100% carotid stenosis
 - usually requires a bypass procedure, as risk of endarterectomy outweighs benefit.
 - previous stroke with persistent neurological symptoms
 - ⇒ Timing of surgery:
 - should be performed within two weeks. ("urgent" endarterectomy within 2 weeks)
 - ⇒ Benefit:
 - It reduces the risk of disabling stroke or death by 48% in a person with severe symptomatic carotid stenosis (>70%) who has had a TIA.
- Carotid stenting
 - ⇒ used as an alternative to endarterectomy: Indications
 - Restenosis.
 - Previous radiotherapy to the neck may make endarterectomy difficult, and stenting may be preferred.

MRCPI-part-2-april-2018: left-sided hemiparesis of more than 8 hours' duration. carotid ultrasound scan, shows 80% stenosis of the left carotid artery, 50% stenosis of the right carotid artery. What is the most appropriate treatment for long-term stroke prevention?

- **⇒** Clopidogrel
 - endarterectomy is not recommended in:
 - significant stenosis but asymptomatic side (left carotid in this case)
 - symptomatic side but there is less than 70% (right carotid in his case).

Carotid artery atherosclerosis is an important cause of ipsilateral amaurosis fugax.

Localisation of speech problems

Only 1 out of 3 features of speech are affected:

- poor <u>comprehension</u> with normal <u>fluency</u> and <u>repetition</u> → <u>Transcortical sensory</u> aphasia
- poor <u>fluency</u> with normal <u>comprehension</u> and <u>repetition</u> → <u>Transcortical motor</u> aphasia
- poor <u>repetition</u> with normal <u>fluency</u> and <u>comprehension</u> → Conduction aphasia

2 out of 3 features of speech are affected:

- Poor <u>comprehension</u> and <u>fluency</u> with <u>normal repletion</u> →Transcortical mixed aphasia
- Poor <u>comprehension</u> and <u>repetition</u> with <u>normal fluency</u> → Wernicke (receptive) aphasia
- Poor <u>fluency</u> and <u>repetition</u> with <u>normal comprehension</u> → Broca's (expressive) aphasia.

All 3 features of speech are affected:

Poor fluency, comprehension and repetition → global aphasia

Overview

- The speech area is in the left, dominant side of the brain in about 99% of right-handed people
- Thus, impairment of the speech area with a stroke, causing left-sided weakness, is rare. It will occur in virtually no right-handers and in only 30% of left-handers.
- As a general rule, a lesion of the left hemisphere will cause dysphasia whilst, in the right hemisphere, it will cause neglect, visuo-spatial and cognitive problems
- Wernicke's aphasia and pure aphasia (that is, without alexia) are middle cerebral artery.
- Comprehension, fluency and repetition are the three main variables that allow for localisation of speech problems
- The three, general, areas are:
 - 1. Wernicke's area (posterior, superior temporal lobe) lesions produce normal fluency, impaired comprehension, impaired repetition
 - receptive aphasia
 - They are unaware of their language difficulties
 - conduction (arcuate fasciculus) lesions produce normal fluency, normal comprehension, diminished repetition
 - 3. Broca's area (inferior frontal lobe)
 - lesions produce impaired fluency, intact comprehension, impaired repetition.
 - Unlike Wernicke's aphasia, Broca's patients are aware of their language difficulties.

	Aphasia Syndromes			
Aphasia	Lesion	Fluency	Comprehension	Repetition
Broca's (expressive)	Broca's area (inferior frontal lobe) superior division of the left middle cerebral artery (MCA) lesion	No	Yes	No
Wernicke (receptive)	(superior temporal lobe) inferior division of the left MCA lesion	Yes	No	No
Conduction	<mark>arcuate fasciculus</mark> peri-Sylvian area	Yes	Yes	No
Transcortical motor	anterior cerebral artery (ACA)-MCA watershed infarct	No	Yes	Yes
Transcortical sensory	posterior cerebral artery (PCA)-MCA watershed infarct	Yes	No	Yes
Transcortical mixed	Can be secondary to both an ACA-MCA and PCA-MCA infarct	No	No	Yes
Global	proximal MCA occlusion affecting both superior and inferior division of the MCA	No	No	No

- Mixed aphasia (or transcortical mixed aphasia)
 - ⇒ patients can often repeat words but not understand commands.
 - ⇒ **Not specific for stroke**, **commonly caused by** Alzheimer's disease, bilateral cerebral damage, tumours, and thalamic lesions.
- Transcortical sensory aphasia
 - ⇒ The main problem lies within the brain in a region known as the **temporal-occipital- parietal junction**, located behind Wernicke's area.
 - ⇒ The patient has intact repetition but is unable to follow verbal commands. He has fluent grammatical speech.
- Anomic aphasia or nominal aphasia results in word finding difficulties.
- Aphemia is a type of aphasia in which there is severe dysarthria and impairment of verbal output. There is intact comprehension.

MRCPUK-part-1-January 2008 exam: H/O difficulty in finding the right words whilst speaking. With normal comprehension. Where is the likely lesion?

⇒ Posterior frontal lobe (expressive aphasia due to a lesion in Broca's area, located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus)

Pupil conditions

Pupillary control

- Oculomotor nerve carries parasympathetic efferent to the sphincter pupillae muscle.
- Optic nerve carries sympathetic postganglionic fibres to the dilator pupillae muscle.

Pupillary control

- Parasympathetic fibers lead to pupillary constriction (miosis)
 - ⇒ light enters the eye → retinal ganglion → optic nerve → optic chiasm → optic tract → pretectal nucleus→ Edinger-Westphal nucleus → ciliary ganglion → pupillary constrictor muscles → causing uniform bilateral miosis
- Sympathetic fibers lead to pupillary dilation (mydriasis)
 - ⇒ hypothalamic nuclei → T1 and T2 spinal cord levels → paravertebral sympathetic chain (via the white ramus) → superior cervical ganglion → pupillary dilator muscle
- Causes of small pupils include:
 - ⇒ Horner's syndrome
 - ⇔ Old age
 - ⇒ Pontine haemorrhage
 - ⇒ Argyll Robertson pupil
 - ⇒ Drugs, and
 - ⇒ Poisons (opiates, organophosphates).
- Causes of dilated pupils include:
 - ⇒ Holmes-Adie (myotonic) pupil
 - ⇒ Third nerve palsy
 - ⇒ Drugs, and
 - ⇒ Poisons (atropine, CO, ethylene glycol).

Pupil	Lesion
Slightly smaller but reactive	Early stage of thalamic damage
Fixed dilatated (7 mm) non-reactive	Oculomotor nerve lesion
Fixed midsized pupil (5 mm)	Midbrain lesion
Pinpoint pupil (1 – 1.5 mm)	Pontine lesion/ opioid overdose
Asymmetrical pupils	Normal in 20% of population but reactive. If one pupil is sluggish to react than the other think of midbrain or oculomotor

· Equality of pupils diameter

- ⇒ Afferent pupillary defect (e.g. optic neuritis) → pupils are isocoric (equal diameter)
- ⇒ **Efferent** (impulse transmission to the iris sphincter muscle) pupillary defect (i.e. impairment of the pupillary reflex) → pupils are **anisocoric** (unequal diameter)

BudgiH

- Hippus is papillary athetosis.(athetosis → abnormal muscle contraction causes involuntary writhing movements).
- It is a spasmodic rhythmical dilation and contraction of the pupil.
- It is typically a benign finding.

Tonic pupil (Holmes-Adie pupil)

Holmes-Adie → dilated pupil

Definition

Tonic pupil or Holmes-Adie pupil is a dilated pupil caused by parasympathetic damage.

Pathophysiology

parasympathetic denervation at the level of the ciliary ganglion and postganglionic nerves.

Causes

- Idiopathic (Most cases)
- · Local causes: infections, trauma
- Systemic autonomic neuropathies
 - ⇒ Ross syndrome is characterized by a triad of tonic pupil, hyporeflexia, and segmental anhidrosis
 - ⇒ Horner syndrome

Features

- Anisocoria (unequal pupil diameter)
 - ⇒ Although the tonic pupil is usually larger than the uninvolved fellow eye, over time the pupil tends to become smaller (the "little old Adie" pupil).
- Hypersensitivity to dilute pilocarpine drops.

Diagnosis

- Clinically: poor pupillary reaction to light + normal test for a pupillary near response (light-near dissociation).
- The usual diagnostic test is to use weak pilocarpine eye drops, which induce vigorous
 pupil contraction on the affected side, but only weak contraction of the pupil on the
 unaffected side.
- Patients with unexplained bilateral tonic pupils should have serologic testing for syphilis

Treatment

• benign condition \rightarrow **observe**

Ross's syndrome: The triad of

- 1. abnormal pupil size,
- 2. loss of deep tendon reflexes, and
- 3. excessive sweating.

Although some doctors will still diagnose the condition as a variant of Holmes-Adie pupil.

Argyll Robertson Pupil (ARP)

Argyll-Robertson

Bilateral small irregular pupils that do not react to light but react to accommodation.

Referred to as the "Whore's Eye" because of the association with tertiary syphilis and because of the convenient mnemonic that, like a prostitute, they "accommodate but do not react"

Causes: neurosyphilis, Multiple Sclerosis, Sarcoidosis, DM



Argyll Robertson Pupil (ARP)

- Bilateral small pupils
- Prostitute's pupils → reduce in size on a near object (they "accommodate"), but do not constrict when exposed to bright light (they do not "react" to light).
- They are a highly specific sign of neurosyphilis and might also be a sign of diabetic neuropathy.

Pupillary Defect	Comments
Argyll Robertson pupil	 Pupils accommodate but do not react to direct or indirect light A type of light-near dissociation where ⇒ Bilateral miosis ⇒ the eye does not constrict in response to light as much as it does with accommodation ⇒ pupil has an absent light reflex Associated with neurosyphilis
Adie's myotonic pupil	A type of light-near dissociation where ⇒ the eye does not constrict in response to light as much as it does with accommodation ⇒ light reflex is merely reduced ⇒ Affected eye is dilated usually Secondary to ⇒ degeneration of the ciliary ganglion

Visual field defects

Visual field defects:

- left homonymous hemianopia means visual field defect to the left, i.e. lesion of right optic tract
- homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)
- incongruous defects = optic tract lesion; congruous defects= optic radiation lesion or occipital cortex

Bitemporal hemianopia:

- · lesion of optic chiasm
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

The main points for the exam are:

- left homonymous hemianopia means visual field defect to the left, i.e. Lesion of right optic tract
- homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)
- incongruous defects = optic tract lesion; congruous defects = optic radiation lesion or occipital cortex
- A congruous defect simply means complete or symmetrical visual field loss and conversely an incongruous defect is incomplete or asymmetric. Please see the link for an excellent diagram.

Homonymous hemianopia

- incongruous defects: lesion of optic tract
- congruous defects: lesion of optic radiation or occipital cortex
- macula sparing: lesion of occipital cortex

Homonymous quadrantanopias

- superior: lesion of temporal lobe
- inferior: lesion of parietal lobe
- mnemonic = PITS (Parietal-Inferior, Temporal-Superior)

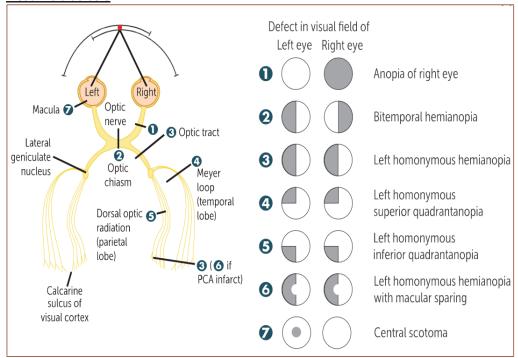
Bitemporal hemianopia

- lesion of optic chiasm
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly
 a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

Cortical blindness

- Patients with cortical blindness frequently have visual hallucinations and occasionally deny that they are blind.
- Pupillary reactions and fundoscopy are normal.

Visual field defects



Bilateral internal carotid artery displacement can cause binasal incongruous hemianopia if the optic nerves are compressed.

MRCP-part-1-September 2012 exam: What sort of visual field defect is expected following an operation to remove a meningioma in left temporal lobe?

→ Right superior homonymous quadrantanopia

Mrcpuk-part-1-January 2009 exam: In a left congruous homonymous hemianopia. Where is the lesion most likely to be?

→ Right occipital cortex

<u>Cranial nerves</u> <u>The major characteristics of the 12 cranial nerves</u>

			Pathway/
Nerve	Functions	Clinical	foramen
l (Olfactory)	Smell		Cribriform plate
II (Optic)	Vision		Optic canal
III (Oculomotor)	Eye movement (MR, IO, SR, IR) Pupil constriction Accommodation Eyelid opening	Palsy results in ptosis 'down and out' eye dilated, fixed pupil	Superior orbital fissure (SOF)
IV (Trochlear)	Supplies superior oblique (SO) → (depresses eye, moves inward)	Palsy results in defective downward gaze → vertical diplopia	SOF
V (Trigeminal)	Facial sensation Mastication	Lesions may cause: trigeminal neuralgia loss of corneal reflex (afferent) loss of facial sensation paralysis of mastication muscles deviation of jaw to weak side	V ₁ : SOF, V ₂ : Foramen rotundum, V ₃ : Foramen ovale
VI (Abducens)	Eye movement (LR)	Palsy results in defective abduction → horizontal diplopia	SOF
VII (Facial)	Facial movement Taste (anterior 2/3rds of tongue) Lacrimation Salivation	Lesions may result in: • flaccid paralysis of upper + lower face • loss of corneal reflex (efferent) • loss of taste • hyperacusis	Internal auditory meatus
VIII (Vestibulocochlear)	Hearing, balance	Hearing loss Vertigo, nystagmus Acoustic neuromas are Schwann cell tumours of the cochlear nerve	Internal auditory meatus
IX (Glossopharyngeal)	Taste (posterior 1/3rd of tongue) Salivation supplies the parotid salivary gland controlling salivary secretions. Swallowing Mediates input from carotid body & sinus	Lesions may result in; • hypersensitive carotid sinus reflex • loss of gag reflex (afferent)	Jugular foramen

Nerve	Functions		Pathway/ foramen
X (Vagus)	Phonation Swallowing Innervates viscera supplies the palatal muscles	Lesions may result in; uvula deviates away from site of lesion loss of gag reflex (efferent)	Jugular foramen
XI (Accessory)	Head and shoulder movement	Lesions may result in; • weakness turning head to contralateral side	Jugular foramen
XII (Hypoglossal)	Tongue movement	Tongue deviates towards side of lesion	Hypogloss al canal

The fourth cranial nerve palsy \rightarrow superior oblique palsy \rightarrow vertical diplopia (eg: missing steps when walking down the stairs, bumping head when trying to get out of a car)

Cranial nerve locations

- 4 CN are above pons (I,II,III,IV).
- 4 CN exit the pons (V,VI,VII,VIII).
- 4 CN are in medulla (IX,X,XI,XII).

Cranial nerve reflexes

Reflex	Afferent limb	Efferent limb
Corneal	Ophthalmic nerve (V₁)	Facial nerve (VII)
Jaw jerk	Mandibular nerve (V ₃)	Mandibular nerve (V ₃)
Gag	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Carotid sinus	Glossopharyngeal nerve (IX)	Vagal nerve (X)
Pupillary light	Optic nerve (II)	Oculomotor nerve (III)
Lacrimation	Ophthalmic nerve (V₁)	Facial nerve (VII)

Brain stem (Mid brain, Pons, Medulla Oblongata) lesions are typically characterized by ipsilateral cranial nerve involvement and contralateral body involvement.

Petrous apex lesion

- Features
 - **⇒** Abducens nerve palsy →horizontal diplopia
 - ⇒ Trigeminal nerve involvement at the Meckel cave → ipsilateral facial pain or sensory disturbance (numbness)
- Causes → Meningioma or nasopharyngeal carcinoma of the petrous apex is the most common cause now

Lesions of the **cerebellopontine angle** causes compression of cranial nerves **V** (trigeminal), **VII** (facial) **and VIII** (vestibulocochlear).

Optic nerve palsy

Anatomy

- The optic nerve is part of the central nervous system; hence its myelin sheaths are derived from oligodendrocytes, not Schwann cells.
- Accordingly, diseases of the peripheral nervous system and radiculopathies don't target the
 optic nerve.
- The physiological blind spot results from absence of photoreceptors in the area of the retina where the optic nerve leaves the eye.

Causes

- · Ischemic optic neuropathy
- multiple sclerosis
- · optic nerve glioma
- ethambutol

Features

- $\bullet \quad \text{Complete transection} \rightarrow \text{ipsilateral blindness and loss of direct pupillary light reflex}$
- Compression (e.g., tumor) → optic atrophy
- Pituitary adenoma → compression to the optic chiasm → bitemporal hemianopia

Oculomotor (third nerve) palsy

```
Ipsilateral 3<sup>rd</sup> CN palsy + contralateral hemiplegia → Weber's syndrome Ipsilateral 3<sup>rd</sup> CN palsy + contralateral hemiataxia → Benedikt syndrome Ipsilateral 3<sup>rd</sup> CN palsy + ipsilateral hemiparesis + Contralateral homonymous hemianopsia → Uncal herniation
```

Compression of the oculomotor nerve can cause isolated pupillary dilation due to injury of the parasympathetic fibers.

Microangiopathy (e.g., due to diabetes mellitus) typically affects the deeper somatic fibers first, causing ophthalmoplegia without pupillary dilation

Features

- Divergent squint affected eve deviated 'down and out'.
 - ⇒ Downward displacement result from unopposed action of the superior oblique (innervated by the fourth cranial or trochlear nerve). due to paralysis of superior rectus, inferior rectus and inferior oblique.
 - ⇒ outward displacement results from unopposed action of the lateral rectus (innervated by the sixth cranial nerve). due to paralysis of the medial rectus muscle.
- Ptosis
- Dilated pupil (mydriasis), sometimes called a 'surgical' third nerve palsy.
 - ⇒ the parasympathetic fibers run on the outside of the nerve. Therefore, 3rd nerve compression → mydriasis appear before ptosis and "down and out" position are seen.
 - ⇒ pupillary abnormalities are more commonly associated with trauma than with ischemia.

- ⇒ A patient with a third nerve palsy with pupillary involvement should be considered to have a posterior communicating artery aneurysm until proven otherwise → requires urgent neurosurgical evaluation.
- Unreactive pupil to light: Lesions of the autonomic (parasympathetic) portion → absence of the pupillary reaction

Causes

- Vascular causes (usually does not affect the pupil): Diabetic neuropathy, vasculitis, Weber's syndrome
- Compressive lesions: Posterior communicating artery aneurysm (painful, pupil dilated) → Urgent CT angiogram of the cerebral vessels is required for diagnosis.
- Cavernous sinus thrombosis
- Others causes: amyloid, multiple sclerosis

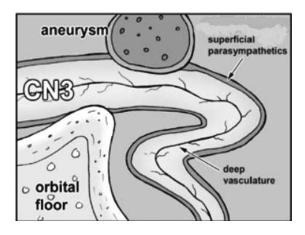
Parasympathetic fibers are located more superficially than motor fibers, causing the following features:

- Prominent motor dysfunction and sparing of the pupil in ischemic lesions due to vascular disease (e.g., vasculitis, diabetes): parasympathetic fibers are less affected by decreased diffusion of nutrients from the vasa nervorum
- Severely impaired pupillary reaction with relatively spared motor function in compressive **lesions** (e.g., uncal herniation, aneurysm of the posterior communicating artery): parasympathetic fibers are affected by compression first

Raised ICP can cause a third nerve palsy due to herniation

Painful third nerve palsy = posterior communicating artery aneurysm





Trigeminal neuralgia

Trigeminal neuralgia - carbamazepine is first-line

Overview

- Sensation over the face is supplied by the trigeminal nerve
- Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain.
- Most often affecting women ♀ > ♂ (2:1)
- Peak age incidence: 60–70 years

Classification

- Idiopathic trigeminal neuralgia
 - ⇒ Most common type
 - ⇒ no identifiable cause (unremarkable findings on MRI and electrophysiological tests)
- Secondary trigeminal neuralgia
 - ⇒ Caused by a major underlying neurological disease, most frequently multiple sclerosis, a tumor at the cerebellopontine angle, or arteriovenous malformation.
 - ⇒ Red flag features suggesting a serious underlying cause
 - Sensory changes
 - Deafness or other ear problems
 - History of skin or oral lesions that could spread perineurally
 - Pain only in the ophthalmic division of the trigeminal nerve (eye socket, forehead, and nose), or bilaterally
 - Optic neuritis
 - A family history of multiple sclerosis
 - Age of onset before 40 years
 - ⇒ Should be referred to neurology
 - ⇒ MRI of the brain is the next management step

Features

- The International Headache Society defines trigeminal neuralgia as: Unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
 - ⇒ Lasts several seconds (in rare cases, several minutes) and may occur up to 100 times per day
 - ⇒ Typically shoots from mouth to the angle of the jaw on the affected side
 - ⇒ Usually **triggered** by movements such as chewing, talking, or touch (e.g., brushing teeth, washing face); becomes worse with stimulation

Management

- · Carbamazepine is first-line
- Failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

MRCPUK-part-1-January 2015 exam: History of electric shock like pains on the right side of the face. around 10-20 episodes a day which, each lasting for around 30-60 seconds. What is the most suitable first-line management?

→ Carbamazepine

What is the nerve supply to the angle of the jaw?

- ⇒ The angle of the jaw is supplied by nerve roots C2/C3 and not the trigeminal nerve.
- ⇒ In patients with non-organic sensory loss, that loss usually extends to the edge of the jaw.

Abducens (VIth) nerve palsy

Anatomy

- Location: The abducens nucleus located in the caudal pons
- Course: The nerve leaves the brainstem at the junction of the pons and medulla and runs
 upward into the subarachnoid space, travelling through the cavernous sinus alongside the
 internal carotid artery. It enters the orbit through the superior orbital fissure, like the other
 ocular cranial nerves, and innervates the lateral rectus, which serves to abduct the eye.
- Function: The VIth nerve is motor to the lateral rectus muscle. It is responsible for abduction of the ipsilateral eye.

Features

- Horizontal diplopia that worsens when looking at distant objects
- · Inability to abduct the eye
- In the neutral position the affected eye is deviated medially due to unopposed action of the medial rectus.
- In patients with diplopia the 'cover test' can be used to determine the eye that has the problem.
 - ⇒ On covering the affected eye, the outermost image disappears.
 - ⇒ Eg : diplopia on right horizontal gaze , improved on covering the right eye →
 the right abducens is affected

Causes

- Most common ocular cranial nerve palsy
- Trauma
- Pseudotumor cerebri
- · Cavernous sinus thrombosis
- Due to the long course and anatomy of the VIth nerve it can be damaged in any condition causing raised intracranial pressure. It can therefore be a 'false localising sign'.

Which nerve passes alongside the internal carotid artery within the cavernous sinus?

Cranial nerve VI, the abducens nerve.



Abducens nerve palsy

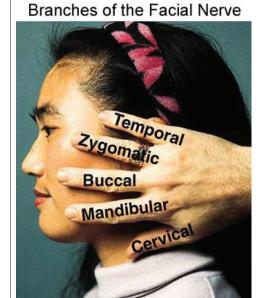
- The patient is unable to abduct the right eye.
- Abducens nerve innervates the ipsilateral lateral rectus muscle that is necessary for lateral movement of the eye.

Facial (VII) nerve

Facial nerve branches (mnemonic)

(superior to inferior) as they exit the anterior border of the parotid gland: To Zanzibar By Motor Car

- 1. T: temporal
- 2. **Z:** zygomatic
- 3. B: buccal
- 4. M: mandibular
- 5. C: cervical



Facial Palsy + convergent squint

Use in Pons
as VI th is encircled by VII th

Facial nerve paralysis is often accompanied by:

- · loss of taste,
- hyperacusis, and
- decreased salivation.

Supply - 'face, ear, taste, tear'

- face: muscles of facial expression
- ear: nerve to stapedius (Hyperacusis is due to paralysis of stapedius)
- · taste: supplies anterior two-thirds of tongue
- · tear: parasympathetic fibres to lacrimal glands, also salivary glands
- Orbicularis oculi is affected causing inability to blink/close eyelids.

Causes of bilateral facial nerve palsy

- 1. Sarcoidosis
- 2. Guillain-Barre syndrome
- 3. polio,
- 4. Lyme disease

Causes of unilateral facial nerve palsy - as above plus

Lower motor neuron	Upper motor neuron
Bell's palsy	Stroke
 Ramsay-Hunt syndrome (due to herpes zoster) 	
Acoustic neuroma	
Parotid tumours	
• HIV	
 Multiple sclerosis* 	
⇒ may also cause an UMN palsy	
Diabetes mellitus	

LMN vs. UMN

- · upper motor neuron lesion 'spares' upper face i.e. forehead
- lower motor neuron lesion affects all facial muscles

Lesions

- The majority of facial nerve palsy cases result from infranuclear lesions.
- The most common cause of facial nerve paralysis is Bell's palsy.

Bell's palsy

Definition

• acute, unilateral, idiopathic, facial nerve paralysis.

Causes

- unknown
- although the role of the herpes simplex virus has been investigated previously.

Epidemiology

- The peak incidence is 20-40 years
- more common in pregnant women.

Features

- lower motor neuron facial nerve palsy forehead affected
- other features
 - ⇒ post-auricular pain (may precede paralysis),

- ⇒ altered taste.
- ⇒ dry eyes.
- ⇒ hyperacusis (seen in around a third of patients)

Management

- prednisolone 1mg/kg for 10 days should be prescribed for patients within 72 hours of onset of Bell's palsy.
- · Adding in aciclovir gives no additional benefit
- eye care is important prescription of artificial tears and eye lubricants should be considered

Prognosis

• if untreated around 15% of patients have permanent moderate to severe weakness

MRCPUK-part-1-January 2012 exam: Which features would be most consistent with a diagnosis of Bell's palsy?

→ Hyperacusis

MRCPUK-part-1-May 2010 exam: What is the current evidenced base approach to the management of Bell's palsy?

→ Prednisolone

Ramsay Hunt syndrome

vesicular rash around the ear (or anterior 2/3rds of the tongue and the soft palate): suggest a diagnosis of Ramsey Hunt syndrome.

Aetiology

• Ramsay Hunt syndrome (herpes zoster oticus) is caused by the **reactivation** of the varicella zoster virus in the **geniculate ganglion** of the seventh cranial nerve.

Features

- auricular pain is often the first feature
- facial nerve palsy
- vesicular rash around the ear
- tinnitus
- vertigo

Management

· oral aciclovir and corticosteroids

Acoustic neuroma

Loss of corneal reflex \rightarrow think acoustic neuroma

Overview

- Acoustic neuromas (more correctly called vestibular schwannomas) are benign tumors of the vestibular nerve (8th nerve).
- account for 5% of intracranial tumours and 90 % of cerebellopontine angle
- Bilateral acoustic neuromas are seen in neurofibromatosis type 2

Features

- · can be predicted by the affected cranial nerves
 - ⇒ cranial nerve V: absent corneal reflex
 - ⇒ cranial nerve VII: facial palsy
 - ⇒ cranial nerve VIII: **hearing loss**, vertigo, **tinnitus**, gait disturbances and imbalance.

Investigation

MRI of the cerebellopontine angle is the investigation of choice → mass

Treatment

· surgical removal remains the treatment of choice

Abnormal gait

Lesions of cerebellar vermis cause → truncal ataxia and tendency to fall backwards.

Phenytoin toxicity → broad-based ataxic gait

Abnormal gait	Diagnosis
Shuffling gait	Parkinson's disease
Spastic hemi-paretic gait (circumducted)	Stroke
Waddling gait (with excessive hip swing)	proximal myopathy
Steppage gait (High stepping, Neuropathic gait)	If bilateral:
Choreiform Gait (Hyperkinetic Gait)	Sydenham's chorea, Huntington's Disease
Ataxic Gait	Cerebellar disease, Phenytoin toxicity
Sensory Gait (Sensory ataxia) occurs when there is loss of this proprioceptive input the patient will slam the foot hard onto the ground in order to sense it.	large fiber peripheral neuropathies

Sensory ataxia is distinguished from cerebellar ataxia by positive Romberg's sign (normal coordination when the movement is visually observed by the patient, and worsened when the eyes are closed)

Nystagmus

Upbeat nystagmus → cerebellar vermis lesions Downbeat nystagmus → foramen magnum lesions (Arnold-Chiari malformation)

Definition

involuntary oscillations of the eyes.

Relation to directions of the gaze

- constant direction regardless of the direction of gaze, suggests → a labyrinthine or cerebellar lesion.
- changes with the direction of gaze suggests widespread central involvement of vestibular nuclei.
- presents only on lateral gaze → lesion of the brain stem or cerebellum.
- Nystagmus restricted to the abducting eye on lateral gaze (ataxic nystagmus) is due to a
 lesion of the medial longitudinal bundle between the pons and mid-brain as in multiple
 sclerosis (MS).

Causes

- Visual disturbances
- Lesions of the labyrinth
- Central vestibular connections, Brain stem or cerebellar lesions
- Wernicke's encephalopathy
- Nystagmus confined to one eye suggests:
 - ⇒ a peripheral lesion of the nerve or muscle,
 - ⇒ or a lesion of the medial longitudinal bundle.

Vertical VS horizontal nystagmus

- · Vertical nystagmus:
 - ⇒ Upbeat nystagmus (occurring on upward gaze: due to a lesion in the mid-brain
 - □ Downbeat nystagmus (fast phase downwards) suggests a lesion in the lower part of the medulla. It is therefore typical of the Arnold-Chiari malformation (Chiari type I malformation).
- Horizontal nystagmus:
 - ⇒ occurs in unilateral disease of the cerebral hemisphere, with the fast phase directed to the side of the lesion.

MRCPUK-part-1-May 2007 exam: Which disorder is most associated with downbeat nystagmus?

→ Arnold-Chiari malformation

Spinocerebellar ataxia (SCA)

Spinocerebellar ataxia (SCA):

- autosomal dominant
- should be suspected in patients with progressive loss of coordination, unsteady gait and overall weakness.

Hemiballism

Hemiballism is caused by damage to the subthalamic nucleus

The presence of severe <u>flinging movements</u> affecting proximal muscles and following no particular pattern is typical for hemiballism.

Overview

- damage to the subthalamic nucleus of the basal ganglia → Hemiballism → decreased suppression of involuntary movements.
- Ballisic movements are involuntary, sudden, jerking movements which occur contralateral to the side of the lesion.
- The ballisic movements primarily affect the proximal limb musculature whilst the distal muscles may display more choreiform-like movements
- It is always unilateral, but it is common for arms and legs to move together.
- Bilateral ballismus is rare and implicates a metabolic cause, usually non-ketotic hyperosmolar coma.
- Symptoms may decrease whilst the patient is asleep.
- The movements worsens with activity and decrease with relaxation.

Causes

- vascular events (stroke). infarction being the commonest cause.
- traumatic brain activity
- · amyotrophic lateral sclerosis
- hyperglycaemia
- malignancy
- · vascular malformations
- · tuberculomas, and
- demyelinating plaques.

Treatment

- tetrabenazine is the treatment of choice.
- Anti-dopaminergic agents (e.g. Haloperidol) are the mainstay of treatment.
- Topiramate can be used, as can intrathecal baclofen, botulinum toxin and tetrabenazine.
- Functional neurosurgery can be used for cases which have failed to respond to other treatment.

Prognosis

Usually the flinging movements stop spontaneously in the next 4-8 weeks

MRCPUK-part-1-September 2012 exam: H/O involuntary, jerking movements of arms, resolved during asleep. Damage to which structure may lead to hemiballism? Subthalamic nucleus

Epilepsy: Classification

Basics

- two main categories are generalised and partial seizures
- partial seizures may progress to general seizures
- other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

Generalised - no focal features, consciousness lost immediately

- Tonic-clonic (grand mal)
- Absence seizures (petit mal)
 - ⇒ absences last a few seconds and are associated with a guick recovery
 - ⇒ mostly seen in children
 - ⇒ 1st line treatment→ ethosuximide
 - ⇒ good prognosis 90-95% become seizure free in adolescence
- myoclonic: brief, rapid muscle jerks
- partial seizures progressing to generalised seizures

Partial - focal features depending on location

- Simple (no disturbance of consciousness or awareness)
- Complex (consciousness is disturbed)
- · Jacksonian seizure
 - ⇒ also known as a focal (partial) motor seizure.
 - ⇒ In this condition an uncontrolled, spontaneous discharge of electricity from one motor cortex presents with contralateral motor signs.
 - ⇒ The patient has preserved consciousness as it is a partial seizure
 - ⇒ after the seizure it is common to have a Todd's paralysis where the limb is weak.

Temporal lobe epilepsy

- ⇒ Focal seizure with impaired awareness (complex partial seizure)
- ⇒ Can take the form of automatisms such as chewing and swallowing repeatedly, scratching the head or searching for an object.
- **⇒** Most commonly arise in the temporal lobes.
- ⇒ MRI is an appropriate investigation
- ⇒ The commonest finding is **hippocampal sclerosis**

Gelastic seizures

- ⇒ Gelastic seizures should be suspected in cases of erratic laughing or crying.
- ⇒ typically arise from **hypothalamic hamartomas**

Absence seizure (petit mal)

- presents with a blank stare, 3 Hz brain waves and do not show postictal confusion.
- Good prognosis: 90 -95% become seizure free in adolescence.

Somatosensory seizures

- Spread of symptoms ('marching') in seconds
- The usual source is the parietal lobe.
- \blacksquare Example \to tingling sensation starts in fingers and spreads in seconds to affect the whole arm and leg.
 - Positive symptoms (jerking, tingling) usually signify epilepsy.
 - Negative symptoms (weakness, numbness) are usually caused by transient focal ischaemia.
- Spread of symptoms ('marching') indicates migraine (in 5-20 minutes) or seizures (in seconds).

Atonic seizure (also known as "drop seizure" or "drop attack")

- Sudden loss of muscle tone: sudden head drop or collapse (lasts < 15 seconds)
- Frequently mistaken for syncope

Epilepsy: investigations

- Electroencephalogram (EEG)
 - ⇒ should be performed only to support a diagnosis
 - ⇒ An EEG should not be performed in the case of probable syncope because of the possibility of a false-positive result.
 - ⇒ should not be used in isolation to make a diagnosis of epilepsy.
 - ⇒ should not be used to exclude a diagnosis of epilepsy in whom the clinical presentation supports a diagnosis of a non-epileptic event.
 - ⇒ can be used to assess the risk of seizure recurrence in patient presenting with a first unprovoked seizure.
 - ⇒ When a standard EEG has not contributed to diagnosis, a sleep EEG should be performed.
 - ⇒ Long-term video or ambulatory EEG may be used in case of diagnostic difficulties after clinical assessment and standard EEG.
- **Neuroimaging:** to identify underlying gross pathology
 - ⇒ MRI is the imaging investigation of choice.
 - ⇒ CT should be used if MRI is not available or is contraindicated.
 - ⇒ In an acute situation, CT may be used to determine whether a seizure has been caused by an acute neurological lesion or illness.
 - ⇒ Neuroimaging should not be routinely requested when a diagnosis of idiopathic generalised epilepsy has been made.

Epilepsy: treatment

Epilepsy medication: first-line

- · generalised seizure: sodium valproate
- · partial seizure: carbamazepine

Patients cannot drive for 6 months following a seizure

When to start antiepileptics?

- Antiepileptics is generally recommended after a second epileptic seizure.
- NICE guidelines suggest starting antiepileptics <u>after the first seizure if</u> any of the following are present:
 - ⇒ the patient has a neurological deficit
 - ⇒ brain imaging shows a structural abnormality
 - ⇒ the EEG shows unequivocal epileptic activity
 - ⇒ the patient or their family or carers consider the risk of having a further seizure unacceptable

Which antiepileptics?

- Focal seizures
 - **⇒** Female of childbearing potential:
 - 1st line → lamotrigine
 - 2^{nd} line \rightarrow levetiracetam
 - 3rd line → oxcarbazepine (can impair the effectiveness of hormonal contraceptives)
 - ⇒ Male or female who are not of childbearing potential:
 - 1st line → lamotrigine or carbamazepine
 - 2nd line → levetiracetam, oxcarbazepine or sodium valproate
- Generalised tonic-clonic (GTC) seizures
 - ⇒ Female of childbearing potential
 - 1st line → lamotrigine
 - 2nd line → levetiracetam, clobazam, or topiramate
 - ⇒ Male or female who are not of childbearing potential
 - 1st line → sodium valproate
 - 2nd line → lamotrigine, carbamazepine, oxcarbazepine
- Absence seizures (Petit mal)
 - ⇒ Female of childbearing potential
 - 1st line → ethosuximide
 - 2nd line → lamotrigine
 - 3rd line → combination of ethosuximide and lamotrigine
 - ⇒ Male or female who are not of childbearing potential
 - 1st line → ethosuximide or sodium valproate
 - 2nd line → lamotrigine
 - 3rd line → combination of two of these three AEDs: ethosuximide, lamotrigine or sodium valproate

- Myoclonic seizures
 - ⇒ Female of childbearing potential
 - 1st line → levetiracetam or topiramate (topiramate can impair the effectiveness of hormonal contraceptives.)
 - 2nd line → add levetiracetam, or topiramate
 - ⇒ Male or female who are not of childbearing potential
 - 1st line → sodium valproate
 - 2nd line → levetiracetam or topiramate

Indications for monitoring of AED blood levels

- detection of non-adherence to the prescribed medication
- suspected toxicity
- adjustment of phenytoin dose
- management of pharmacokinetic interactions (for example, changes in bioavailability, changes in elimination, and co-medication with interacting drugs)
- specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy

Stopping of anti-epileptic drugs (AED)

- Can be considered if seizure free for at least 2 years, with AEDs being stopped slowly over 2-3 months (withdrawing benzodiazepines and barbiturates may take up to 6 months or longer)
- Benzodiazepines should be withdrawn over a longer period.

Vagus nerve stimulation

• indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication

If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy (JME) is suspected, do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin.

AED cessation can be considered if seizure free for > 2 years - Stop AEDs over 2-3 months

MRCPUK-part-1-January 2015 exam: Which one of the antiepileptic drugs is most associated with weight gain? Sodium valproate

MRCPUK-part-1-September 2012 exam: What is the most appropriate first-line antiepileptic for myoclonic seizures? Sodium valproate

Antiepileptic drugs (AED)

Overview

- Only start after a minimum of two fits.
- Only use one drug at a time, and begin with a small dose, and gradually increase it, until control is achieved, toxic affects occur, or the maximum dose is reached.
- The diagnosis of epilepsy needs to be critically evaluated if events continue despite an optimal dose of a first-line AED.
- If the initial treatment is unsuccessful, then monotherapy using another drug can be tried.

 If an AED has failed because of adverse effects or continued seizures, a second drug should be started (which may be an alternative first-line or second-line drug) and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.

Drug	Mechanism	Side effects	Clinical uses
Benzodiazepines	↑ GABA action	Sedation, tolerance, dependence, respiratory depression	1 st line for acute
Phenobarbital	↑ GABA action	Sedation, impairment of motor and cognition systems after long term use, megaloblastic anaemia	Rarely used due to sedation – been superseded by phenytoin
Phenytoin	Inhibits sodium channels Blocks Na+ channels ;zero-order kinetics	Gum hypertrophy, arrythmias Cytochrome P-450 induction, Pseudo-lymphoma, Hirsutism, Nystagmus, Yellow-brown skin, Teratogenicity (fetal hydantoin syndrome), Osteopenia, Inhibited folate absorption, Neuropathy. Rare: SJS, DRESS syndrome, drug-induced lupus. Toxicity leads to diplopia, ataxia, sedation.	Partial and generalised attacks, but not in absence. High doses my precipitate attacks
Carbamazepine	Inhibits sodium channels	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, SJS, skin rash	1 st line for partial seizures. 2 nd or 3 rd line, when other drugs unsuccessful.
Ethosuximide	Blocks thalamic T- type Ca2+ channels	Fatigue, Headache, Itching, SJS	Useful for absence seizures
Lamotrigine	Blocks voltage-gated Na+ channels, inhibits the release of glutamate	SJS (must be titrated slowly), hemophagocytic lymphohistiocytosis (black box warning)	Generalised seizures – 2 nd line treatment
Sodium valproate	 ↑Na+ channel inactivation ↑GABA concentration by inhibiting GABA transaminase 	Alopecia, Hepatotoxic, Pancreatitis, P-450 inhibition (reduces efficacy of contraceptive pill), Rash, Weight gain, Tremor, Teratogenesis (neural tube defects).	 1st line for: Absence seizures & Generalised seizures 2nd line for partial seizures
Levetiracetam	 SV2A receptor blocker; May modulate GABA and glutamate release, Inhibit voltage-gated Ca2+ channels 	Neuropsychiatric symptoms (eg, personality change), fatigue, drowsiness, headache	For partial and generalised

Which antiepileptic drugs does not have interactions with warfarin?

- Lamotrigine has no effect on liver enzymes and is the treatment of choice for patient taking warfarin
- Phenytoin, carbamazepine, primidone and phenobarbital are liver enzyme inducers
- Sodium valproate is a liver enzyme inhibitor

If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures.

Which antiepileptic drug is most likely to cause renal stones side-effects?

→ Topiramate (The side effects of topiramate include: weight loss, renal stones and cognitive and behaviour changes).

MRCPUK-part-1-September 2008 exam: H/O complex partial seizures, not able to tolerate either carbamazepine or sodium valproate. What is the most appropriate next line drug?

→ Lamotrigine

What is the likelihood of controlling seizures in a patient never previously on anti-epileptic medication?

A study of patients with previously untreated epilepsy demonstrated that:

- With a single first-line anti-convulsant agent \rightarrow 47% achieved control of seizures
- 14% became seizure-free during treatment with a second or third drug.
- An additional 3% became seizure-free with the use of two drugs simultaneously.

Carbamazepine and oxcarbazepine but be aware of the risk of exacerbating myoclonic or absence seizures

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy is the **most common** primary generalised epilepsy, but is underdiagnosed due to lack awareness of the condition by doctors

Overview

- is a common form of idiopathic generalised epilepsy, representing 10% of all patients with epilepsy.
- typically, first manifests itself between the ages of 10 and 20 with brief episodes of involuntary muscle twitching occurring early in the morning.

Genetic

• The condition is genetically linked to the short arm of chromosome 6.

Presentation

- Bilateral symmetrical myoclonic jerks, primarily after awakening, without impaired consciousness
- Generalized tonic-clonic seizures
- Absence seizures with impaired consciousness
- Myoclonic jerks, especially of the upper limbs, which predominantly occur in the mornings shortly after waking (and may be so subtle as to be interpreted as 'clumsiness' when eating breakfast)
- Triggers: sleep deprivation, alcohol consumption, flickering lights

Investigations

Interictal EEG is diagnostic showing → generalised spike- and polyspike-wave activity; a
photosensitive response may also be present

Management

- Female of childbearing potential
 - ⇒ 1st line → lamotrigine, levetiracetam or topiramate
 - ⇒ 2nd line → add lamotrigine, levetiracetam or topiramate
- Male or female who are not of childbearing potential
 - ⇒ 1st line → sodium valproate
 - ⇒ 2nd line → add lamotrigine. levetiracetam, or topiramate

Prognosis

 Prognosis is extremely favourable if the condition is treated correctly, with many patients becoming seizure-free.

Status epilepticus

Definition

 ≥5 minutes of continuous seizure activity, or more than one seizure without recovery in between

Treatment

- Initial management: ABC. Maintain airway and circulation with intubation
- 1st line anticonvulsant: two doses of benzodiazepines (Lorazepam is preferred).
- 2nd line anticonvulsant: parenteral anti-epileptics (<u>intravenous phenobarbital or phenytoin</u>
 - ⇒ **Fosphenytoin**: (a pro-drug of phenytoin)

- advantages over phenytoin:
 - ❖ it can be given IV or IM (phenytoin can only be given IV)
 - can be given at infusion rates three times faster than phenytoin
 - therapeutic levels are achieved within 10 minutes
 - it has a lower incidence of adverse events than phenytoin.
 - If the patient is already taking phenytoin, either IV phenytoin or fosphenytoin should still be given: it is likely that plasma levels are subtherapeutic.
- ⇒ Phenytoin is not recommended in patients with underlying liver impairment therefore not used in status epilepticus secondary to alcohol withdrawal.
- 3rd line: ICU for general anaesthesia (Midazolam or propofol)
 - ⇒ **Monitoring:** By **EEG** in unconscious patients to differentiate between sedation and nonconvulsive seizures → EEG pattern:
 - Focal or focal with secondary generalization → nonconvulsive status epilepticus
 - Generalized slowing, attenuation, lateralizing periodic discharges → postictal.

The use of phenytoin is not recommended in patients with underlying liver impairment therefore not used in status epilepticus secondary to alcohol withdrawal.

If a patient in generalised status epilepticus does not respond to lorazepam and adequate doses of intravenous phenytoin, what is the next step in their management?

→ Transfer to an Intensive Therapy Unit

Epilepsy: pregnancy and breast feeding

Epilepsy + pregnancy = 5mg folic acid

Overview

- Epilepsy is not a contraindication to pregnancy.
- the risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus

Risk of congenital defects

- Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to **3-4%** if the mother takes antiepileptic medication.
- All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy until at least the end of the first trimester to minimise the risk of neural tube defects.

What is the effect of pregnancy on epilepsy?

- Two-thirds will not have seizure deterioration in pregnancy
- The overall chance of postpartum seizures is relatively higher than during pregnancy.

Management

- Exposure to sodium valproate and other AED polytherapy should be minimised by changing the medication **prior to conception**.
- We suggest NOT making changes to antiseizure drug regimen for the purpose of reducing teratogenic risk in established pregnancy
- Aim for monotherapy. The lowest effective dose of the most appropriate AED should be used.
- Some women who have been seizure free for a prolonged period may reasonably choose to discontinue antiseizure drug prior to conception.
- Women with epilepsy taking AEDs who become unexpectedly pregnant: It is never recommended to stop or change AEDs abruptly without an informed discussion.
- the **levetiracetam** has a favorable reproductive safety profile and has a broad spectrum of action across multiple seizure types.
- If seizures are focal and begin after the first trimester, carbamazepine is another option.
 (carbamazepine often considered the least teratogenic of the older antiepileptics)
- Sodium valproate should not be used during pregnancy and in women of childbearing age unless she is on a pregnancy prevention programme. Associated with neural tube defects and neurodevelopmental delay.
- · Phenytoin:
 - ⇒ associated with cleft palate
 - ⇒ It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn.
- Lamotrigine:
 - ⇒ the rate of congenital malformations may be low.
 - ⇒ The dose of lamotrigine may need to be increased in pregnancy
- **Breast feeding** is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

Pseudoseizures

Suspected psychogenic non-epileptic seizures → do Video-EEG recording

Overview

- Pseudoseizures are commonly misdiagnosed as true seizures and treated inappropriately with anti-epileptic drugs.
- patients of any age can present with pseudoseizures.
- features such as tongue biting and urinary incontinence are not absolute features of an organic seizure, they are often present in pseudoseizures.

Factors favouring pseudoseizures

- · pelvic thrusting
- family member with epilepsy
- more common in females
- accompanying underlying psychiatric concerns, e.g. crying after seizure, tearful around the time of the seizure.
- attacks in public and absence of nocturnal events (don't occur when alone)

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- · gradual onset
- prolonged nature of the attacks (15-30 minutes)
- Violent shaking
- · resistance to passive eye opening
- · very short post-ictal state
- · normal vital signs

Urinary incontinence can also occur in pseudoseizures, but tongue biting is rare

Factors favouring true epileptic seizures

- tongue biting
- · raised serum prolactin

Diagnosis

Video telemetry is useful for differentiating

Treatment

• Simple observation is the appropriate management.

Rett syndrome

Overview

- Rett syndrome is a neurodevelopmental disorder of the <u>grey matter</u>
- inherited as an X-linked dominant disorder.
- mostly affecting girls.
 - ⇒ Males affected by Rett syndrome die in utero or shortly after birth.
- related to the <u>MECP2 gene on the X chromosome</u>

Feature

- Small hands and feet with deceleration of head growth.
- Epileptic → repetitive hand movements such as hand wringing.
- · loss of development, verbal abilities and cognition, ataxia
- · GI problems, such as constipation.

Tourette syndrome

Definition

a chronic neurologic disorder that manifests with motor and vocal tics

Epidemiology

- Tourette syndrome presents before 18 years of age and many children grow out of it.
- more common in males (4:1)

Pathogenesis

- due to genetic, environmental, and social factors resulting in an abnormality in the mesolimbic spinal system
- the condition is familial in most cases

Features

- The motor tics often have a build-up that the patient is aware of, like an itch.
- . Commonly they involve blinking, throat clearing or shoulder shrugging.
- Shouting of swear words is a typical vocal tic of Tourette's.

Associated conditions

 90% of patients have a comorbid psychiatric disorder such as attention deficit hyperactivity disorder (~60% of cases)

Management

- first-line: Cognitive behavioural therapy
- Second line: pharmacotherapy alpha-2 agonist (e.g., clonidine and guanfacine).

Huntington's disease (HD)

Pathophysiology

- Autosomal dominant →Increased number of CAG repeats (trinucleotide repeat disorder) in the huntingtin gene on chromosome 4 (coding for glutamine) → formation of abnormal proteins which have abnormal number of glutamine residues (huntingtin) → degeneration of GABAergic neurons (gamma-amino-butyric acid-ergic neurons in the striatum (particularly in the caudate nucleus) of the basal ganglia.
- The striatum normally controls movement via inhibitory outputs to the globus pallidus internus.
- Anticipation: increase in the number of CAG repeats in subsequent generations (The
 disease may develop earlier in life in each successive generation)

Epidemiology

Symptom onset usually between 20 and 50 years of age

Features

- Personality changes (e.g. irritability, disinhibition, apathy, depression) and intellectual impairment (the earliest symptom)
- Chorea
 - Athetosis is a hyperkinetic movement symptom characterized by slow, involuntary, writhing movements. Huntington disease and cerebral palsy are the most common causes.
- · Lack of coordination and an unsteady gait
- Dystonia
- Saccadic eye movements
- Dementia
- Dopamine levels are increased
- Gamma-aminobutyric acid levels are decreased
- Acetylcholine levels in the central nervous system are decreased

Diagnosis

- . DNA analysis is the most useful diagnostic test
 - ⇒ (e.g., via PCR)
 - ⇒ Trinucleotide CAG repeat expansion in the Huntington gene is diagnostic
- MRI → caudate nucleus atrophy
 - ⇒ Atrophy of the caudate nucleus, putamen, and deep cerebral cortex are the hallmark features of Huntington's disease.
 - ⇒ Hvdrocephalus ex vacuo
 - Hydrocephalus ex vacuo is an expansion of the cerebral ventricles and surrounding subarachnoid space caused by atrophy of the underlying brain tissue, and not an expansion of CSF volume primarily.

⇒ The role of neuroimaging is primarily to rule out other intracranial causes of a patient's symptoms, rather than to diagnose HD.

Treatment

- Tetrabenazine and reserpine works as a VMAT-inhibitor (vesicular monoamine transporter 2), involved in transportation of monoamines. It is indicated for Huntington's chorea to reduce hyperkinetic movements.
- Haloperidol is a dopamine-2 antagonist used to treat movement disorders, hallucinations, and delusions in Huntington disease.

Prognosis

- progressive and incurable
- Average life span after clinical onset is about 15 years (premature death).

In Huntington disease, increased number of CAG repeats leads to the damage to the Caudate nucleus and results in decreased acetylcholine (Ach) and GABA.

Cluster headache

Cluster headache - acute treatment: subcutaneous sumatriptan + 100% O2

Epidemiology

- More common in men (5:1) and smokers.
- More common in younger males below the age of 40

Features

- pain typical occurs once or twice a day, each episode lasting 15 mins 2 hours
- clusters typically last 4-12 weeks
- intense pain around one eye (recurrent attacks 'always' affect same side)
- The attacks are often nocturnal and are associated with parasympathetic overactivity.
- patient is restless during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

Management

- Acute: 100% oxygen, subcutaneous or a nasal triptan
 - ⇒ the use of 100% oxygen at least 12 litres per minute via a non-rebreathable mask
 - ⇒ It is not recommended to offer paracetamol, NSAIDS, opioids, ergots or oral triptans for the acute treatment of a cluster headache.
- prophylaxis: First line → verapamil, prednisolone, with other options including lithium, sodium valproate and gabapentin
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging



Cluster headaches may involve pain around one eye, along with drooping of the lid, tearing and congestion on the same side as the pain

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Differential diagnosis

• The main differential is between cluster headaches and **chronic paroxysmal hemicrania** (CPH; which is treated with indomethacin).

Distinguishing cluster headaches and Chronic Paroxysmal Hemicrania

Cluster headache	Chronic Paroxysmal Hemicrania
more common in males	more common in females
frequency of attacks is 1 - 4 (maximum 8) in 24 hours.	the frequency of attacks is higher , usually more than 15 in 24 hours
The duration of headaches is (15-60 min).	The duration of headaches is shorter (2-25 min)
Not responds to indomethacin	responds very well to indomethacin

Migraine

Diagnostic criteria

The International Headache Society has produced the following diagnostic criteria for **migraine** without aura:

Point	Criteria
Α	At least 5 attacks fulfilling criteria B-D
В	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)
С	Headache has at least two of the following characteristics: 1. unilateral location 2. pulsating quality (i.e., varying with the heartbeat) 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D	During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia
E	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

NICE suggests migraines may be unilateral or bilateral

Migraine with aura

- seen in around 25% of migraine patients
- tends to be easier to diagnose with a typical aura being progressive in nature
- may occur hours prior to the headache.
- Typical aura include:
 - ⇒ transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent').
 - ⇒ Spreading (over minutes) sensory and motor symptoms
 - ⇒ Word-finding difficulties are also a common migraine aura symptom.
 - ⇒ autonomic symptoms such as a Horner syndrome
 - ⇒ negative auras of dark holes and tunnel vision
 - ⇒ Dizziness and fatigue are quite common prior to a migraine attack
 - ⇒ Patients may have mixed positive and negative auras.
 - ⇒ Positive auras include bright or shimmering light or shapes at the edge of their field of vision called scintillating scotoma. They can enlarge and fill the line of vision. Other positive aura experiences are zigzag lines or stars.
- may occur with or without headache
- NICE also give more detail about typical auras:
 - > are fully reversible
 - develop over at least 5 minutes

- ➤ last 5-60 minutes
- The following aura symptoms are atypical and may prompt further investigation/referral;
 - ⇒ motor weakness

 - ⇒ visual symptoms affecting only one eye
 - ⇒ poor balance
 - ⇒ decreased level of consciousness.
- Complicated migraine
 - Complicated migraine is one which results in hemi sensory or hemi motor findings associated with a typical migraine presentation.
- Confusional migraine involves alteration in sensorium rather than limb involvement.

Other features:

- family history of similar headaches is common
- Bilateral fortification spectra
 - ⇒ Fortification spectra (jagged lines resembling battlements) and teichopsia (flashes) are common features of migraine.
- Precipitation by oral contraceptives (contraindicated in migraine with aura)
- Frequency reduced by tricyclic antidepressants (can be useful in the prophylaxis of migrain)
- Third nerve palsy
 - ⇒ seen in **ophthalmoplegic migraine**
 - ⇒ ophthalmoplegic migraine was reclassified as a <u>cranial neuralgia</u> in the most recent International Headache Society classification.
 - ⇒ most commonly affects the third nerve.
 - ⇒ the deficits can be permanent.
 - ⇒ A subset of these patients will have gadolinium enhancement of the cisternal segment of the cranial nerve
 - ⇒ it is thought some of these patients actually have a demyelinating neuropathy.

Migraine: management

Migraine

- acute: triptan + NSAID or triptan + paracetamol
- prophylaxis: topiramate or propranolol

acute → 5-HT agonists

prophylaxis: β-blocker, 5-HT2 antagonist

- 5-HT receptor agonists are used in the acute treatment of migraine
- 5-HT receptor antagonists are used in prophylaxis.

Acute treatment

- first-line:
 - ⇒ combination of oral triptan and NSAID, **OR** oral triptan and paracetamol
 - for young people aged 12-17 years: nasal triptan is preferred than oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide* or prochlorperazine and consider adding a non-oral NSAID or triptan
 - ⇒ *caution should be exercised with young patients as acute dystonic reactions may develop with metoclopramide.

Prophylaxis

- prophylaxis should be given if patients are experiencing 2 or more attacks per month.
- Modern treatment is effective in about 60% of patients.
- NICE advise either topiramate or propranolol or amitriptyline 'according to the person's preference, comorbidities and risk of adverse events'.
 - Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives
- if these measures fail NICE recommend 'a course of up to 10 sessions of <u>acupuncture</u> over 5-8 weeks'
- gabapentin are not recommended now because evidence shows that it is not effective in preventing migraine. (NICE 2015)
- NICE recommend: 'Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
 - ⇒ riboflavin also known as vitamin B₂
 - safe during pregnancy.
- for women with **predictable menstrual migraine** treatment:
 - ⇒ NICE recommend either frova**triptan** (2.5 mg twice a day) or zolmi**triptan** (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- · pizotifen is no longer recommend.
 - ⇒ Adverse effects such as weight gain & drowsiness are common

Efficacy of Paracetamol in migraine

- Migraine → ↓ gastric emptying → ↓Paracetamol absorption → ↓Paracetamol effects
- Metoclopramide may be useful in accelerating gastric emptying.
- paracetamol absorption technique is used to study gastric emptying.

MRCPUK-part-1-January 2006 exam: Which type of medication would be most appropriate to reduce the frequency of migraine attacks?

→ **Beta-blocker** (Topiramate is also recommended by NICE as first-line prophylaxis against migraine. However, a beta-blocker is a better choice in a female of child-bearing age)

Migraine: pregnancy, contraception and other hormonal factors

Migraine during pregnancy

- paracetamol 1g is first-line
- · aspirin 300mg or ibuprofen 400mg can be used second-line in the first and second trimester

Migraine and the combined oral contraceptive (COC) pill

• if patients have migraine with aura then the COC is absolutely contraindicated due to an increased risk of stroke (relative risk 8.72)

Migraine and menstruation

- many women find that the frequency and severity of migraines increase around the time of menstruation
- SIGN recommends that women are treated with mefanamic acid or a combination of aspirin, paracetamol and caffeine. Triptans are also recommended in the acute situation

Migraine and hormone replacement therapy (HRT)

safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

Triptans

Action

- Triptans are specific **5-HT1 agonists** used in the acute treatment of migraine.
- They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points

- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

• 'triptan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications

 patients with a history of, or significant risk factors for, ischaemic heart disease or cerebrovascular disease

Epilepsy is not a contraindication to the use of triptans

Idiopathic intracranial hypertension(IIH)

Obese, young female with headaches / blurred vision : think idiopathic intracranial hypertension

Postural headache but normal imaging → idiopathic intracranial hypertension

Suspected Idiopathic intracranial hypertension \rightarrow lumbar puncture to confirm the diagnosis is the next step

Overview

- also known as pseudotumour cerebri and formerly benign intracranial hypertension
- · classically seen in young, overweight females.

Risk factors

- obesity
- female sex
- pregnancy
- drugs:
 - oral contraceptive pill (eg: Dianette),
 - ⇒ Danazol (synthetic androgen used to treat endometriosis)
 - ⇒ steroids.
 - ⇒ tetracycline,
 - ⇒ vitamin A,
 - ⇒ Nalidixic acid
 - ⇒ *if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

Features

- headache
 - ⇒ chronic postural headache (suggested by its improvement as the day progresses)
 - ⇒ 10% of cases are free of headaches.
- blurred vision, (Horizontal diplopia)
 - ⇒ Diplopia is common due to sixth nerve palsy.
- papilloedema (usually present)
- · enlarged blind spot
- Reduction in colour vision is common
- · sixth nerve palsy may be present
- normal appearances of the magnetic resonance imaging (MRI). Normal ventricular size, anatomy and position. Normal CSF cell count and protein content.
- plantars are flexor
 - ⇒ Extensor plantars suggest alternative diagnosis.
- · Absence of retinal venous pulsations

Diagnosis

- the diagnosis is confirmed by finding an elevated CSF opening pressure (more than 20 cm H₂O). CSF protein, glucose and cell count will be normal.
- CT and MRI scans are often normal
 - CT brain is needed to exclude a space occupying lesion and obstructing hydrocephalus.
 - ➡ MRI venogram is recommended afterwards to exclude cerebral sinus thrombosis.

Management

- · weight loss
- · diuretics e.g. acetazolamide
- topiramate (anticonvulsant) is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery:
 - ⇒ A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure
 - ⇒ optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve.
 - In progressive visual loss → Lumbo-peritoneal (LP) shunt is the treatment of choice.
 - Optic nerve fenestration is an alternative.
 - There are no comparative studies between the two interventions.

Complication

Progressive visual loss and optic atrophy

Scenario

A young, obese female presents with a progressive blurring in her vision over the last 12 months but **denies any headache**. on fundoscopy she has bilateral blurred and **heaped up optic discs** which are obviously **pale**. CT head scan was reported as normal. Which appropriate investigation for this patient?

→ Brain MR venography

- The description of the pale but prominent optic discs goes with early secondary optic atrophy and hence should promote a search for a cause for a longstanding papilloedema.
- she is likely to have idiopathic intracranial hypertension; 10% of cases are free of headaches.
- The next most appropriate investigations would be assessment for any
 underlying causes and include magnetic resonance venography (MRV)
 (exclude cerebral sinus thrombosis) and cerebrospinal fluid (CSF) analysis
 with assessment of the opening pressure and other CSF parameters as a
 confirmatory step.

MRCPUK-part-1-September 2008 exam: Sudden loss of vision in left eye + headaches + bilateral papilloedema. Which drug is most likely to be responsible?

→ Prednisolone → intracranial hypertension

Spontaneous intracranial hypotension (SIH)

Strong postural relationship with the headache generally much worse when upright and easy with lying horizontal. Patients may therefore be bed-bound

Definition

- Low (CSF) pressure headache, (< 6 cm CSF)
- The lower limit of the normal range for CSF pressure is 10 cm H2O

Causes

- The most common cause → following lumbar puncture,
 - ⇒ The leak is typically from the thoracic nerve root sleeves.
- Other possible causes:
 - following an episode of possible minor trauma to meninges (eg sports injury to neck or back)
 - ⇒ without apparent cause (SIH).

Mechanism and features

- CSF leak leads to → low CSF pressure → orthostatic headache in association with one or more of the following symptoms:
 - ⇒ nausea, vomiting
 - ⇒ horizontal diplopia
 - ⇒ unsteadiness or vertigo
 - ⇒ altered hearing
 - ⇒ neck pain/stiffness
 - ⇒ interscapular pain
 - ⇒ visual field abnormalities

Diagnosis

- CSF opening pressure at lumbar puncture:
 - ⇒ opening CSF pressure is low, (< 6 cm CSF), and often a 'dry' tap is encountered
 - ⇒ However, the pressure may be normal
 - ⇒ CSF fluid analysis is normal
- MRI with gadolinium
 - ⇒ confirming the diagnosis
 - demonstrates distinctive dural gadolinium enhancement and downward displacement of brain on sagittal views.
 - ⇒ typically reveal diffuse pachymeningeal enhancement, frequently in association with 'sagging' of the brain, tonsillar descent and posterior fossa crowding

Treatment

- usually conservative (first-line): bed rest, analgesia, increased fluid intake
- if this fails an epidural blood patch may be tried

Medication overuse headache

Medication overuse headache

- Simple analgesia + triptans: stop abruptly
- Opioid analgesia: withdraw gradually

Definition

a headache occurs ≥ 15 days per month due to overuse of headache medication (e.g. opioid, paracetamol, triptans and NSAIDs) for > 3 months.

Epidemiology

• Prevalence: 1 to 2% and is higher in females than males.

Features

- A history of symptomatic medication use more than two to three days per week in association with chronic daily headache is suggestive.
- · Commonly occurs daily or nearly daily.
- Butalbital-containing analgesics and opioids has the highest risk of medication overuse headache.

Management

- Simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- Opioid analgesics should be gradually withdrawn
- Withdrawal symptoms are likely to occur, including worsening headache, nausea, agitation
 and sleep disturbance. These usually settle within seven days, and headaches should stop
 within approximately three weeks.
- While discontinuing the overused medication, some patient may require bridge therapy such as long-acting NSAIDs; eq. naproxen or oral prednisone.

Parkinsonism

Definition

• Parkinsonism refers to clinical syndromes that mimic the symptoms of Parkinson's disease (PD) (e.g. tremor, bradykinesia, rigidity).

Causes

- Parkinson disease (PD): Idiopathic
- Secondary parkinsonism
 - ⇒ Drug-induced e.g. antipsychotics, metoclopramide
 - ⇒ Progressive supra-nuclear palsy
 - ⇒ Multiple system atrophy
 - ⇒ Wilson's disease
 - ⇒ Post-encephalitis
 - ⇒ Dementia pugilistica (secondary to chronic head trauma e.g. boxing)
 - ⇒ Toxins: carbon monoxide, MPTP
 - **⇒** Drugs-induced Parkinsonism
 - Phenothiazines: e.g. chlorpromazine, prochlorperazine
 - Butyrophenones: haloperidol, droperidol
 - Metoclopramide
 - Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects

Parkinson's disease (PD)

Parkinson's disease - most common psychiatric problem is depression

Definition

• Progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra.

Epidemiology

- The second most common neurodegenerative disorder following Alzheimer disease
- Prevalence is 1-2 per 1000 people
- More common in men (2:1)
- Mean age of diagnosis is 65 years

Risk factors

- Advanced age (>60 years)
- · Family history
- Male sex
- Environmental pesticides.

Pathophysiology

- In normal circumstances
 - ⇒ There are two pathways in the brain that promote motion, the direct (stimulatory) pathway and the indirect (inhibitory) pathway.
 - ⇒ In normal circumstances, the stimulatory pathway is activated while the inhibitory pathway is deactivated, allowing for smooth motion.
 - ⇒ Dopamine <u>stimulate</u> the <u>Direct Pathway</u> and <u>inhibits</u> the <u>Indirect Pathway</u>.
 - □ The substantia nigra (part of the basal ganglia) produces dopamine, which binds the
 □1 receptors in the striatum, inhibiting the globus pallidus, leading to activation
 of the thalamus and allowing movement (activation of the direct stimulatory
 pathway)
 - ⇒ Also, dopamine binds the D2 receptor, inhibiting the inhibitory pathway (inhibition of the indirect pathway).
- In Parkinson disease
 - \Rightarrow Aggregates of α -synuclein proteins \rightarrow form Lewy bodies \rightarrow loss of the dopamine-producing neurons in the substantia nigra.
 - ⇒ Decreased dopamine causes **increased inhibitory output** from the **globus pallidus** via both the direct and indirect pathways → _motion.
 - ⇒ ↓ dopamine → ↓activation of D1 receptor on striatum → ↓excitatory (stimulatory) direct pathway → ↑ globus pallidus internus output → ↓thalamic function → ↓motion.
 - ⇒ ↓ dopamine → ↓ activation of D2 receptor on striatum → disinhibiting the inhibitory pathway
 - ⇒ The classical signs of bradykinesia, resting tremor and rigidity start to appear after approximately 50% of the dopamine neurons, and 75-80% of striatal dopamine is lost.

Decreased dopamine impairs movement by which mechanisms?

Decreased activation of the D1 and D2 receptors

Which mechanism underlying the neurodegeneration seen in Parkinson's?

- Impaired protein degradation
- Mutations in either the parkin gene or UCHL1 lead to impaired protein degradation.
- → Alpha-synuclein is a synaptic protein accumulates in Lewy body dementia and Parkinson's disease.

What is the characteristic microscopic finding in Parkinson's disease?

Lewy body

Features

The classic triad of features: bradykinesia, tremor and rigidity

The symptoms of Parkinson's disease are characteristically asymmetrical.

Bradykinesia

- ⇒ poverty of movement also seen, sometimes referred to as hypokinesia
- ⇒ short, shuffling steps with reduced arm swinging
- ⇒ difficulty in initiating movement

Tremor

- ⇒ most marked at rest, 3-5 Hz
- ⇒ worse when stressed or tired
- ⇒ typically, 'pill-rolling', i.e. in the thumb and index finger
- ⇒ The tremor of parkinsonism only disappears during REM sleep.

Rigidity

- ⇒ lead pipe
- ⇒ cogwheel: due to superimposed tremor

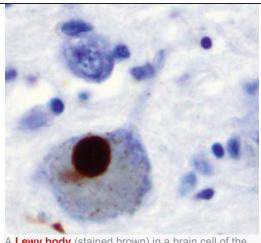
Other characteristic features

- ⇒ mask-like facies
- ⇒ flexed posture

- ⇒ psychiatric features:
 - depression is the most common feature (affects about 40%);
 - dementia, psychosis and sleep disturbances may also occur
- ⇒ impaired olfaction
- **⇒** REM sleep behaviour disorder
 - The earliest feature (During REM sleep, the patient may be seen kicking, laughing, punching, or fighting invisible enemies.)
- **⇒** Intestinal pseudo-obstruction
 - a common feature of advanced Parkinson's
 - results in symptoms of <u>intermittent abdominal bloating and vomiting</u>.

Drug-induced parkinsonism differs from Parkinson's disease in:

- motor symptoms are generally rapid onset and bilateral
- rigidity and rest tremor are uncommon



A **Lewy body** (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein.





Discoloration of the substantia nigra due to **loss of pigmented nerve cells**.

Diagnosis: Diagnostic criteria for Parkinson's disease

- · Step 1. Diagnosis of a parkinsonian syndrome
 - ⇒ Bradykinesia and at least one of the following:
 - Muscular rigidity
 - Rest tremor (4-6 Hz)
 - Postural instability unrelated to primary visual, cerebellar, vestibular, or proprioceptive dysfunction
- Step 2. Exclusion criteria for Parkinson's disease
 - ⇒ History of:
 - Repeated strokes with stepwise progression
 - Repeated head injury
 - Antipsychotic or dopamine-depleting drugs
 - Definite encephalitis or oculogyric crises on no drug treatment
 - More than one affected relative
 - Sustained remission
 - Negative response to large doses of levodopa (if malabsorption excluded)
 - Strictly unilateral features after 3 years
 - Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory, or praxis
 - Exposure to known neurotoxin
 - Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

Step 3. Supportive criteria for Parkinson's disease

- ⇒ Three or more required for diagnosis of definite Parkinson's disease:
 - Unilateral onset
 - Excellent response to levodopa
 - Rest tremor present
 - Severe levodopa-induced chorea
 - Progressive disorder
 - Levodopa response for over 5 years
 - Persistent asymmetry affecting the side of onset most
 - Clinical course of over 10 years.

Feature most strongly suggest idiopathic Parkinson's disease \rightarrow asymmetry of tremor

Investigations

- Single photon Emission Computed Tomography (SPECT)
 - ➡ The investigation of choice for people with tremor if essential tremor cannot be clinically differentiated from parkinsonism.

Management

General rule of treatment:

- Starting dopamine agonists such as ropinirole for younger patients under 65.
- Saving L-dopa for later in the disease while reducing the long-term risk of motor complications.

Levodopa should be offered for patients with newly diagnosed Parkinson's who have motor symptoms affecting their quality of life

First-line treatment

- \Rightarrow If the motor symptoms are affecting the patient's quality of life \rightarrow levodopa
- ⇒ If the motor symptoms are not affecting the patient's quality of life → non-ergot dopamine agonist (e.g., ropinirole, apomorphine), levodopa or monoamine oxidase B (MAO-B) inhibitor (e.g., selegiline)
- ⇒ Patients > 65 years or multimorbid patients of any age → levodopa PLUS decarboxylase inhibitor (carbidopa): due to inevitable motor complications that is associated with levodopa.
- ⇒ Patients < 65 years with no significant comorbidities → Non-ergot dopamine agonists (e.g., pramipexole, ropinirole, apomorphine)

Second line

- ⇒ Adjuvant treatment of motor symptoms (dyskinesia and/or motor fluctuations) if not responded despite optimal levodopa therapy → Add non-ergot-derived dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors (e.g., entacapone)
- Third line
 - ⇒ If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine
- Fourth- line \rightarrow deep brain stimulation
 - ⇒ For advanced Parkinson's disease, whose symptoms are not adequately controlled by best medical therapy
 - ⇒ Targets: subthalamic nucleus or internal globus pallidus
 - ⇒ In the context of suicidal behaviour, the patient would not be a candidate for deep brain stimulation, which for unknown reasons, increases the risk of suicide.

Comparison between anti-Parkinson drugs

- Improvement in motor symptoms and activities of daily living.
 - \Rightarrow **Levodopa** \rightarrow **More** improvement
 - ⇒ Other antiparkinsonian medicines (e.g. Dopamine agonists, MAO-B inhibitors & COMT inhibitors) → Less improvement
 - **⇒** Amantadine → No evidence of improvement
- Off time (periods of the day between medication doses when the medication is not working well, causing worsening of Parkinsonian symptoms).
 - ⇒ Dopamine agonists → More off-time reduction
 - ⇒ Amantadine → No studies reporting this outcome
- Adverse events
 - ⇒ Levodopa, MAO-B inhibitors & COMT inhibitors → Fewer adverse events
 - **⇒** Dopamine agonists → Intermediate risk of adverse events
 - ⇒ Amantadine → No studies reporting this outcome
- Motor complications
 - ⇒ Levodopa → More motor complications
 - **⇒** Dopamine agonists & MAO-B inhibitors → Fewer motor complications
- Hallucinations
 - ⇒ Levodopa, MAO-B inhibitors & COMT inhibitors → Lower risk
 - **⇒** Dopamine agonists → More risk
 - ⇒ Amantadine → No studies reporting this outcome

Of the antiparkinson drugs, levodopa is associated with the greatest improvement in symptoms and activities of daily living

Management of non-motor symptoms of Parkinson's disease

- $\bullet \quad \text{Excessive daytime sleepiness} \to \mathsf{modafinil}$
- Rapid eye movement sleep behaviour disorder \rightarrow clonazepam or melatonin
- **Nocturnal akinesia** → levodopa or oral dopamine agonists
- Postural hypotension
 - ⇒ Review the possible pharmacological causes, e.g. antihypertensives (including diuretics), dopaminergics, anticholinergics, antidepressants.
 - ⇒ First line → midodrine (alpha agonist): monitor for supine hypertension.
 - ⇒ Second line → **fludrocortisone** (If midodrine is not tolerated or not effective).

Psychotic symptoms (hallucinations and delusions)

- ⇒ Do not treat if they are well tolerated.
- ⇒ Reduce the dosage of any Parkinson's disease medicines
- ⇒ Consider **quetiapine** (in people without cognitive impairment) or **clozapine**.
- ⇒ **Do not** offer olanzapine

Dementia

- ⇒ 1st line: cholinesterase inhibitor (**rivastigmine**, donepezil, or galantamine capsules or rivastigmine patches)
- ⇒ 2nd line: if cholinesterase inhibitors are not tolerated or contraindicated → memantine

Drooling

- ⇒ 1st line: glycopyrronium bromide (anticholinergic) → reduce excessive saliva (sialorrhea) & does not cross the blood–brain barrier → no central effects.
- \Rightarrow 2nd line: If glycopyrronium bromide is not effective \rightarrow referral for botulinum toxin

Parkinson's medication withdrawal

- Antiparkinsonian medicines should not be withdrawn abruptly or allowed to fail suddenly
 due to poor absorption (for example, gastroenteritis, abdominal surgery) to avoid the
 potential for acute akinesia or neuroleptic malignant syndrome.
- The practice of withdrawing people from their antiparkinsonian drugs (so called 'drug holidays') to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome.

• Parkinsonian malignant syndrome

- ⇒ Triggered by abrupt withdrawal from anti-parkinsonian medication.
- ⇒ The presentation is similar of neuroleptic malignant syndrome (pyrexia, rigidity, tachycardia) but without a history of neuroleptic drug use.
- ⇒ Re-initiation of Parkinson's therapy is curative.

Anti-Parkinson drugs

Levodopa (L-DOPA)

Mode of action

- ⇒ Precursor to dopamine, can penetrate the blood brain barrier (peripherally administered dopamine cannot penetrate the blood brain barrier)
- □ Converted to dopamine by DOPA decarboxylase at the presynaptic neuron → direct dopaminergic effect

Indication

⇒ First-line treatment for patients > 65 years of age or patients with comorbidities. Second-line treatment for patients < 65 years of age.

Administration

Normally combined with a peripheral decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine (levodopa alone → peripheral conversion of levodopa to dopamine → significant GI side effects such as nausea and vomiting).

Advantages

⇒ Most effective drug for reducing symptoms

Disadvantages

- ⇒ Increased risk of severe motor dysfunction: levodopa-induced dyskinesia (LID)
 - \rightarrow involuntary writhing movements: choreiform movements, dystonia, myoclonus, and ballism). Peak-dose dyskinesia is most common:
 - Due to higher dose of levodopa.
 - Usually involve upper limbs, trunk, and orofacial muscles.
 - Treatment: reduction of levodopa dose (use frequent smaller dosage)
 - Amantadine is an NMDA antagonist and considered the most effective drug used for LID.
- ⇒ Reduced effectiveness with time (usually by 2 years)
- ⇒ On/off effect (phenomena)
 - due to long-standing chronic levodopa therapy and seen when the serum level of levodopa is least.
 - usually manifest as abnormal spasm of body parts, which most commonly affect foot or leg and rarely present on the arm or trunk.
 - Off-period dystonia usually occurs at night or early morning
 - Treatment
 - may be improved either by the addition of cabergoline (a dopamine agonist) or a subcutaneous infusion of apomorphine.
 - Liquid forms of I-dopa may also be helpful as they allow closer titration of dose, and splitting meals into smaller snacks.

Side effects

- ⇒ Nausea & vomiting , dry mouth, anorexia
- ⇒ Cardiac arrhythmias, postural hypotension
- □ Drowsiness
- ⇒ Reddish discolouration of urine upon standing
- ⇒ Psychosis, hallucinations (usually visual)
 - usually appear late (more than two years after initiation of treatment).
 - The risk for developing psychiatric symptoms increases with age, other psychiatric conditions, long duration of levodopa treatment, and high doses.
- ⇒ Levodopa can increase intraocular pressure, therefore it is not recommended in patients with glaucoma.
- Not used in neuroleptic induced parkinsonism

Dopamine receptor agonists

Ropinirole - dopamine receptor agonist

Agents

- Non-ergot dopamine agonists agents: Ropinirole, apomorphine, pramipexole, rotigotine
- ⇒ Ergot-derived dopamine agonists: bromocriptine, cabergoline, pergolide (not recommended as first-line treatment for Parkinson's disease).
- Action: Act directly at striatal dopamine receptors
- Indication
 - ⇒ First-line treatment for patients < 65 years of age
 - ⇒ Adjunctive treatment for patients of any age

- Advantage: Fewer motor side effects
- Disadvantage: Less effective than L-DOPA
- Side effects
 - ⇒ Nausea, orthostatic hypotension, daytime drowsiness (somnolence)
 - ⇒ **Psychotic symptoms: Hallucinations**, psychosis, impulse control disorders
 - impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating and obsessive shopping). If modifying dopaminergic therapy is not effective → cognitive behavioural therapy
 - ⇒ Dopamine agonist withdrawal syndrome
 - ⇒ **Ergot dopamine agonists: fibrosis** (cardiac, pulmonary, retriperitoneal)
 - retroperitoneal fibrosis → obstruction of both ureters → bilateral hydronephrosis → chronic kidney disease
 - echocardiogram, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

MAO-B (Monoamine Oxidase-B) inhibitors

- Agents: Selegiline, Rasagiline, Safinamide.
- Action: inhibits the breakdown of dopamine secreted by the dopaminergic neurons
 - ⇒ Selective inhibition of MAO-B → ↓ metabolization of dopamine into DOPAC in the brain → prolonged dopamine availability and effect→ ↓ demand for L-DOPA
- Indication
 - ⇒ Alternative to L-DOPA or dopamine agonists
 - \Rightarrow Can also be given in combination with L-DOPA $\rightarrow \downarrow$ motor fluctuations
- Side effects: Headache, dyskinesia, psychological disorders (e.g., hallucinations)

NMDA antagonists (Amantadine)

- Action
 - ⇒ Acts antagonistically at the glutamate N-methyl-D-aspartate (NMDA) receptor →
 dopaminergic effect
 - ⇒ ↑ Dopamine release and ⊥ dopamine reuptake in central neurons
- Indication
 - ⇒ Short-term treatment of mild symptoms
 - ⇒ Drug of choice during akinetic crisis
 - ⇒ Reduction of L-DOPA-induced dyskinesia
- Side-effects
 - ⇒ ataxia, slurred speech, confusion, dizziness
 - ⇒ livedo reticularis
 - ⇒ **peripheral edema** (should be avoided in congestive heart failure)

COMT (Catechol-O-Methyl Transferase) inhibitors

- Agents: Entacapone, tolcapone
- Action
 - ⇒ Inhibition of catechol-O-methyltransferase (COMT) → ↓ peripheral metabolization of L-DOPA to 3-O-methyldopa (3-OMD) → ↑ availability
 - ⇒ Tolcapone also prevents central COMT from breaking down dopamine to 3methoxytyramine (3-MT) by crossing the blood-brain barrier → ↑ dopamine effect →
 ↓ demand for L-DOPA and longer therapeutic effect for each dose
- Indication: used in conjunction with levodopa. COMT inhibitor monotherapy is ineffective; therefore, it should always be combined with L-DOPA and carbidopa.

Anticholinergic drugs (muscarinic antagonists)

- Agents: Procyclidine, Benztropine, Trihexyphenidyl (benzhexol), Biperiden
- Action: Inhibition of excitatory cholinergic neurons →
 ↓ concentration of acetylcholine
- Indication
 - □ Useful as monotherapy in patients < 65 years of age with tremor as the main symptom
 </p>
 - ⇒ Help tremor and rigidity but does not improve bradykinesia.
 - ⇒ Now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
 - ⇒ Usually avoided in patients > 65 years because they are more prone to anticholinergic side effects (e.g., urinary retention, delirium, constipation)

MRCPUK-part-1-January 2017 exam: H/O schizophrenia, developed parkinsonism secondary to his antipsychotic medication. Which drug is most useful in the management of tremor?

→ Benzhexol

MRCPUK-part-1-January 2018 exam: What is the mechanism of action of selegiline in Parkinson's disease?

→ Monoamine Oxidase-B inhibitor

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy:

• the triad of parkinsonism, vertical gaze palsy and cognitive impairment

Overview

- · aka Steele-Richardson-Olszewski syndrome
- a 'Parkinson Plus syndrome

Features

- Impairment of vertical gaze (especially downward gaze patients may complain of difficultly reading or descending stairs)
- Parkinsonism
- Postural instability leading to frequent falls (often first symptom); retropulsion (falling backward on a pull test) is characteristic
- Slurring of speech (pseudobulbar palsy)
- Cognitive impairment: frontal lobe abnormalities (apathy, disinhibition, impaired reasoning)
- Dementia

Diagnosis

• MRI: "hummingbird sign" showing atrophy of midbrain structures with a relatively intact pons region

Management: poor response to L-dopa **Prognosis:** usually fatal within 5–10 years

Multiple system atrophy (MSA)

Multiple system atrophy: a triad of

- Parkinsonism
- Autonomic disturbance (atonic bladder, postural hypotension)
- Cerebellar signs (e.g., ataxia, tremor, dysarthria)

Overview

- Shy-Drager syndrome is a type of multiple system atrophy.
- The average age of onset is 50 years (earlier than in Parkinson's disease)
- The median survival six to nine years.
- It runs a briefer course than Parkinson's disease.

Pathology

- Macroscopic: most commonly atrophy of olivopontocerebellar and striatonigral systems
- · Microscopic: glial cytoplasmic inclusions

Features

- Parkinsonism
- Autonomic disturbance (urinary incontinence (atonic bladder), postural hypotension, erectile dysfunction)
- Cerebellar signs (e.g., ataxia, tremor, dysarthria)
- Myoclonus, dystonia, ocular motility disorders, pyramidal signs

Treatment: Only symptomatic treatment

MRCPUK-part-1-May 2019 exam: A 67-year-old increasing clumsiness + ataxic gait + ↑↑upper limb tone with cog-wheel rigidity. Blood pressure is 135/80 lying and 95/70 standing. What is the most likely diagnosis?

→ Multiple system atrophy

Corticobasal degeneration (a Parkinson-plus syndrome) characterised by:

- Dementia
- · Asymmetric motor abnormalities, often initially affecting only one limb
- Alien limb phenomenon: involuntary but purposeful movement of the limb PLUS feeling that the affected limb does not belong to the patient and acts on its own.

Differential diagnoses of Parkinson-plus syndromes				
Multiple system atrophy	Progressive	Corticobasal	Dementia with	
	supranuclear palsy degeneration		Lewy bodies	
Autonomic dysfunction with urogenital problems	Vertical gaze palsy Frontal lobe disturbances	Asymmetric motor symptoms Alien limb phenomenon	Lewy bodiesVisual hallucinations	

Normal pressure hydrocephalus (NPH)

Normal pressure hydrocephalus

Classic triad of urinary incontinence, dementia, and gait apraxia.

Overview

 Normal pressure hydrocephalus is a reversible cause of dementia seen in elderly patients.

Mechanism

- It is thought to be secondary to reduced CSF absorption at the arachnoid villi.
- \downarrow CSF absorption \rightarrow CSF accumulation \rightarrow enlargement of the ventricle

Causes

- Idiopathic (most common in adults > 60 years)
- May be secondary to head injury, subarachnoid haemorrhage or meningitis

Features: the triad of

- 1. urinary incontinence
- 2. dementia and bradyphrenia
- 3. gait abnormality (may be similar to Parkinson's disease)

Diagnosis

- Imaging: MRI (initial test), CT
 - ⇒ Ventriculomegaly without sulcal enlargement
 - ⇒ Hydrocephalus with an enlarged fourth ventricle
- CSF tap test: confirmatory test
 - ⇒ Opening pressure is normal or slightly elevated.
 - ⇒ Improvement of symptoms after CSF removal via lumbar puncture or shunt confirms NPH.
 - ⇒ Lumbar puncture is both diagnostic and therapeutic.

Management

- the most likely helpful initial managements steps is CSF drainage via repeated lumbar puncture
- ventriculo-peritoneal shunting

What is the underlying cause of urinary incontinence in NPH?

- Inability to suppress voiding
 - NPH → compression of the periventricular white matter tracts → functional frontal lobe impairment → loss of central inhibition of the detrusor muscle → strong voiding reflex that cannot be suppressed (urge incontinence).

Delirium (Acute confusional state)

Definition

 Delirium: a syndrome of acute confusion characterized by fluctuations in awareness, cognition, and attention

Risk factors

- Age ≥ 65 years
- Cognitive impairment (past or present) and/or dementia
- · Current hip fracture
- Severe illness: affect up to 30% of all older patients admitted to hospital.

Causes

- DELIRIUM: Drugs, Electrolyte abnormalities, Lack of medication (withdrawal), Infection,
 Reduced sensorial input, Intracranial pathology, Urinary retention or fecal impaction,
 Myocardial and pulmonary disease
- Delirium is frequently a complication of dementia.

Features

- **Cognitive function:** e.g., worsened concentration, slow responses, confusion, memory disturbances (loss of short term > long term).
- Perception: e.g., visual or auditory hallucinations.
- Physical function: e.g., reduced mobility, restlessness, agitation, sleep disturbance.
- Social behaviour: e.g., lack of cooperation with reasonable requests, withdrawal, mood change

Diagnosis

- The Confusion Assessment Method (CAM) is the most effective tool in identifying delirium.
- If there is difficulty distinguishing between the diagnoses of delirium, dementia or delirium superimposed on dementia, treat for delirium first.

Management

- Treatment of underlying cause
- Agitation should initially be managed with nonpharmacologic strategies, verbal and non-verbal techniques to de-escalate the situation (e.g., modification of environment).
- Medications should be reserved for refractory agitation.
 - ⇒ the 2019 NICE delirium guidelines recommend short-term **haloperidol** 0.5 mg (usually for ≤1 week).
 - ⇒ Avoid antipsychotic drugs in Parkinson's disease or dementia with Lewy bodies
- If delirium does not resolve: Re-evaluate for underlying causes, assess for possible dementia

MRCPUK-part-1-January 2011 exam: An elderly patient admitted for UTI, became agitated and aggressive. What is the most appropriate management?

→ Haloperidol 0.5 mg orally

Dementia

Overview

- Dementia affect over 700,000 people in the UKT
- DP43 is a protein that has recently been found to be involved in a multitude of neurodegenerative diseases including dementia and motor neuron disease.

Common causes of dementia

- Alzheimer's disease (> 50% of dementia cases)
- Multi-infarct dementia due to cerebrovascular disease (20% of dementia cases)
- Lewy body dementia (c. 10-20%)

Rarer causes (5% of cases)

- Huntington's
- CJD
- Pick's disease (atrophy of frontal and temporal lobes)
- HIV (50% of AIDS patients)

Features

- Mini-mental state examination. A score of 24 or less out of 30 suggests dementia
- Short term memory impairment is the commonest clinical presentation of Alzheimer's disease.
- The best way to test short term memory is to ask the patient to recall new information in the next few minutes.
- · Long term memory is usually intact.
- Usually patients are fully orientated in time, person and place.

Distinguishing between normal aging and dementia

- Memory impairment, occasional difficulties in word finding, and slower cognitive processing are normal effects of aging.
- An important distinguishing factor between normal aging and forms of dementia is the
 degree to which independence with everyday activities is impaired. In normal aging,
 independence in daily activities is preserved.
- cognitive exams are within normal limits in aging.
- Alzheimer's disease is often accompanied by behavioral changes (such as aggression, depression, insomnia)

Investigations

Neuroimaging is required to diagnose dementia

- Exclude reversible secondary causes e.g., hypothyroidism, FBC, U&E, LFTs, calcium, glucose, TFTs, vitamin B12 and folate levels.
- Neuroimaging to exclude other cerebral pathologies (e.g. Subdural haematoma, normal pressure hydrocephalus) and to help establish the subtype diagnosis.(CT could be used, but MRI is better)

- Single-photon emission computed tomography (SPECT) should be used to differentiate
 Alzheimer's disease, vascular dementia and frontotemporal dementia if the diagnosis
 is in doubt.
- Cerebrospinal fluid examination should be used if Creutzfeldt–Jakob disease or other forms of rapidly progressive dementia are suspected.

Vascular dementia

- Typically occurs in those with widespread vascular disease. A history of strokes or the presence of focal neurological signs are very suggestive.
- CT or MRI will show → multiple lacunar infarcts
- Does not respond to acetylcholinesterase inhibitors such as donepezil.
- Vascular dementia caused by lipohyalinosis or microatheroma formation and NOT thromboemboli. Therefore, anticoagulation is not indicated.
- Memory therapy is the best next step in management for patient's confirmed vascular dementia.

Presence of the e4 allele of apo-lipoprotein E → Alzheimer's disease

Loss of GABA is seen in \rightarrow Parkinson's disease.

Peri-vascular mononuclear inflammation is seen in \rightarrow multiple sclerosis.

Loss of Betz cells is seen in \rightarrow motor neurone disease.

Alzheimer's disease (AD)

Overview

- Alzheimer's disease is a progressive degenerative disease of the brain and it is the common cause of dementia.
- Typically, first affects the temporal and parietal lobes
 - ⇒ **Temporal lobe** degeneration results in memory loss (misplaced keys, leaving the stove on) and language deficits (word-finding difficulties).
 - ⇒ whereas parietal lobe degeneration results in spatial navigation problems (getting lost during walks outside)
- The primary anatomical target of Alzheimer's disease is → the cerebral cortex
 - ⇒ Alzheimer's disease is a form of "cortical" type of dementia
 - ⇒ The "sub-cortical type" of dementia occurs in Huntington's disease, advanced Wilson's disease, and advanced multiple sclerosis

Genetics

- · Most cases are sporadic
- Early-onset (before the age of 65) familial AD represents ~ 10% of all AD cases
- Mutations in presenilin 1 (PSEN1)
 - ⇒ Linked to ~ 50% of familial AD cases
 - ⇒ earlier onset compared to AD due to mutations of other genes (median is ~ 43 years)
- Amyloid precursor protein (APP) gene
 - ⇒ Linked to 10–15% of early-onset familial AD cases
 - ⇒ Since the APP gene is located on chromosome 21, individuals with trisomy 21 have an increased risk of early-onset AD (around age 50) due to APP overexpression

Pathological changes

- Macroscopic: widespread cerebral atrophy, particularly involving the cortex and hippocampus
- Microscopic: cortical plaques due to deposition of type A-Beta-amyloid protein and intraneuronal neurofibrillary tangles caused by abnormal aggregation of the tau protein
- **Biochemical:** there is a **deficit of acetylcholine** from damage to an ascending forebrain projection
 - ⇒ ↓production of choline acetyl transferase → ↓acetylcholine synthesis → ↓cortical cholinergic functioning

Features

- Short-term memory impairment (the most common presentation) of AD dementia (insidious onset, slow progression, episodic memory affected first)
- Language impairment
- Temporal and spatial disorientation (patients are usually not oriented to person, place, time, or events)
- · Impairment of executive functions and judgment
- Behavioral changes (apathy, agitation, aggression, irritability)
- Mood disorders (e.g., symptoms of depression)

Investigations

- Screening for B12 deficiency and hypothyroidism
- MRI or CT to rule out reversible causes of cognitive decline
 - ⇒ MRI scan in Alzheimer → symmetrically **increased size of the lateral ventricles** along with **cerebral cortical atrophy** in a mainly frontal and parietal distribution.
 - ⇒ Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans.
- FDG-PET (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable
- Examining cerebrospinal fluid for:
 - ⇒ total tau or total tau and phosphorylated-tau 181
 - ⇒ amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40.

Management

- Non-pharmacological: should always be attempted prior to resorting to pharmacologic treatment.
 - ⇒ **Memory therapy** for all dementias: involves improving cognitive abilities through image recognition, solving math problems, and past memory recall.
 - ⇒ Behavioral and environmental regulation, such as:
 - adhering to a regular sleep schedule
 - Maintaining a consistent environment will help orient the patient. Frequent travel has been shown to worsen the symptoms of Alzheimer's disease.
- Mild to moderate Alzheimer's disease: acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine)
 - ⇒ A well-known side effect of rivastigmine is AV block
 - ⇒ NICE guidelines recommend discontinuation of cholinesterase inhibitors once the mini mental state examination has fallen below 12.
 - ⇒ There is no role for cholinesterase inhibitors in advanced Alzheimer's disease.
 - NICE guidelines recommend discontinuation of cholinesterase inhibitors once the mini mental state examination has fallen below 12.

- The best option would be to withdraw donepezil and possibly consider memantine, which is licensed for use in moderate to severe dementia.
- **⇒** Side-effects of cholinesterase inhibitors
 - Bradycardia and, rarely, AV block
 - Bladder outflow obstruction
- Moderate to severe Alzheimer's: memantine (a NMDA receptor antagonist)
- Management of aggression in dementia
 - ⇒ 1st line: non-pharmacological: identify and avoid triggers + behavioural techniques.
 - ⇒ 2nd line: pharmacological:
 - Olanzapine or quetiapine for short-term
 - Risperidone has been tested in this setting and is licensed for 6 weeks treatment of persistent aggression in those with moderate to severe Alzheimer's disease
 - For patients with dementia with Lewy bodies (DLB), only very low doses of certain atypical neuroleptics (eg, quetiapine or clozapine) should be used due to high risk of severe side effects with neuroleptic medications.

Lewy body dementia (LBD)

Lewy body dementia: a triad of: Dementia, parkinsonism, and visual hallucinations

Epidemiology

• Second most common form of neurodegenerative dementia (10–20% of dementia cases)

Pathology

- **Macroscopic:** Cerebral atrophy, particularly of the frontal lobe. Relative sparing of the hippocampi
- Microscopic: Lewy bodies: alpha-synuclein-positive, hyaline cytoplasmic inclusions in neurons (mostly cortical) that cause neuronal degeneration The characteristic pathological feature is alpha-synuclein cytoplasmic inclusions (Lewy bodies) in the substantia nigra, paralimbic and neocortical areas

Features

- Progressive cognitive impairment
- Parkinsonism
- Visual hallucinations
- Intermittent confusion
- Myoclonus
- Marked sensitivity to neuroleptic treatment.

Diagnosis

- usually clinical
- Single-photon emission computed tomography (SPECT) is increasingly used. The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%

Differential diagnosis: Parkinson's disease with dementia VS Lewy body dementia

- Lewy body dementia presents with signs similar to Parkinson's Disease, but cognitive symptoms precede the motor symptoms.
 - Lewy body dementia if the onset of both cognitive and motor symptoms is within 1 year
 - ⇒ Dementia secondary to Parkinson disease if cognitive symptoms occur > 1 year after the onset of motor symptoms

Treatment

Haloperidol is contra-indicated in Lewy body dementia

- The treatment of choice is rivastigmine, which improves both the visual hallucinations, and cognitive impairment.
- Neuroleptics should be avoided in Lewy body dementia, as patients are extremely sensitive and may develop irreversible parkinsonism.
 - Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent
 - The most appropriate therapeutic strategy with respect to maintaining his mobility is → Stop dopamine-blocking drugs (causing significant parkinsonism) eg: quetiapine

MRCPUK-part-1-September 2018 exam: A 78-year-old man with memory impairment, hallucinations, resting tremor, festinating gait and an expressionless face. He scores 12 / 30 on the mini-mental state examination (MMSE). which test is most likely to confirm the diagnosis?

→ SPECT scan (Lewy body dementia)

MRCPUK-part-1-September 2017 exam: H/O parkinsonian symptoms + agitation. deteriorated after prescribing haloperidol. What is the most likely underlying diagnosis?

→ Lewy body dementia

Frontotemporal lobar degeneration (FTLD)

Overview

- Heterogeneous group of syndromes that involve degeneration of the frontal, insular, and/or temporal cortices
- FTD is sometimes still referred to as Pick disease
- The third most common type of cortical dementia after Alzheimer's and Lewy body dementia.
- Age of onset: typically younger than in Alzheimer disease

Pathology

 Generally associated with pathological intracellular inclusion bodies (Pick bodies) that are caused by mutations in tau (main protein component of Pick bodies) or progranulin (precursor of granulin, which regulates cell growth) proteins.

The inclusions found histologically in frontotemporal dementia, or Pick's disease are hyperphosphorylated tau proteins.

Features

- Onset before 65
- Insidious onset
- Personality change and social conduct problems (apathy, disinhibited behavior)
- Relatively preserved memory and visuospatial skills
- Changes in cognitive functioning: Aphasia
- CT/MRI: atrophy of the frontal and/or temporal lobes

Types: There are three recognised types of FTLD

- Frontotemporal dementia (Pick's disease)
 - ⇒ This is the most common type of frontotemporal dementia
 - ⇒ characterised by personality change and impaired social conduct.
- Progressive non-fluent aphasia (chronic progressive aphasia, CPA)
 - ⇒ Here the chief factor is non-fluent speech. They make short utterances that are agrammatic.
 - ⇒ Comprehension is relatively preserved.
- Semantic dementia
 - ⇒ Here the patient has a fluent progressive aphasia. The speech is fluent but empty and conveys little meaning.
 - ⇒ Unlike in Alzheimer's memory is better for recent rather than remote events.

Patients with FTD display changes of personality and social behavior, but their memory generally remains intact.

Treatment

- No curative treatment.
- Dementia: Cholinesterase inhibitors and memantine are usually not effective
- Agitation, hallucinations, insomnia: Atypical antipsychotics

Creutzfeldt-Jakob disease (CJD)

Rapidly progressive dementia and myoclonic jerks are the hallmarks of Creutzfeldt-Jakob disease.

Definition

 Creutzfeldt-Jakob disease (CJD) is rapidly progressive neurological condition caused by prions that are resistant to degradation by <u>proteases</u> due to misfolding into beta-pleated sheets. <u>prion</u> is an <u>incorrectly folded protein</u> that causes <u>misfolding</u> of other proteins.

Epidemiology

• CJD is the most common prion disease in humans.

Causes and types

- Sporadic (~ 85%): no identifiable cause
- Familial (\sim 10–15%): various mutations in the PRNP gene
- Acquired (< 1%)
 - ⇒ **latrogenic CJD**: transmission during medical procedures (e.g., via organ transplantation, blood transfusion)

- Variant CJD (vCJD): by ingestion of beef infected with bovine spongiform encephalopathy (BSE)
 - BSE is a transmissible prion disease occurring in cattle. Infection leads to vCJD in humans.)

Pathophysiology 1 4 1

Conversion of normal cellular prion proteins with alpha-helical structure (PrPc) to prions that
demonstrate an increase in beta-pleated sheet structure (PrPSc) (insoluble, misfolded
prions resistant to proteases)→ PrPSc accumulation→ plaque formation → neuronal cell
death → progression to spongiform encephalopathy

What is the agent responsible for variant Creutzfeldt-Jakob disease (CJD)?

→ Proteinaceous infectious particle (prion protein)

Features

- Rapidly progressing dementia (weeks to months)
- Myoclonus
- Cerebellar disturbances (e.g., gait instability, ataxia)
- Pyramidal weakness
- · Behavioural abnormality
- · Akinetic mutism.

Investigation

- **CSF analysis**: ↑ 14-3-3 protein → useful in confirming a diagnosis of sporadic CJD.
- MRI: shows high-signal abnormalities (hyperintense signals) in caudate nucleus and putamen or at least 2 cortical regions (temporal-parietal-occipital)
- EEG:
 - ⇒ biphasic, high amplitude sharp waves (only in sporadic CJD)
 - ⇒ EEG is usually normal in new variant CJD.
- Brain biopsy
 - ⇒ Diagnosis can only be confirmed by biopsy/autopsy
 - ⇒ Microscopic findings include spongiform degeneration , amyloid plaques (vCJD)

Types

Form	Features		
Sporadic caused by (Unknown cause)	 Account for 85% of cases Occur at middle-age (mean age of onset is 65 years) Median duration of disease is 5 months 		
Genetic caused by (Mutation in PRNP gene)	 Can occur at younger ages Family history can be negative Dementia usually occur late in the course of the disease Often no detectable 14-3-3 protein in CSF Median duration of disease is several years 		
latrogenic caused by (Transmission of prion protein by invasive medical treatment)	Similar as sporadic form		
Variant caused by (Ingestion of contaminated products with bovine spongiform encephalopathy)	 Occurs at a young age (median age 25 years) Psychological symptoms such as anxiety, withdrawal and dysphonia are the most common initial presenting features Ataxia, myoclonus appear late (6 months after psychological symptoms) EEG is usually normal MRI brain typically shows bilateral pulvinar (posterior thalamic nuclei) high signals. Median duration of disease is 13 months 		

The rapidly progressive neurological impairment, with myoclonus and hyper-reflexia coupled with EEG abnormality and MRI changes in the caudate and putamen, is most consistent with sporadic CJD.

Treatment

- No curative therapy available
- Symptomatic treatment and eventually palliative care

Prognosis

Following disease manifestation, most individuals with sporadic CJD die within 12 months, usually from complications such as pneumonia.

Transient global amnesia

Definition

· Transient loss of memory function

Pathophysiology

• Aetiology is unknown, thought to be due to transient ischaemia to the thalamus (in particular the amygdala and hippocampus)

Risk factors

- Usually affects people over the age of 50
- Psychological and physical stress

Diagnostic criteria

- **Abrupt onset** of amnesia (anterograde or partial retrograde)
- · Patients may appear anxious and repeatedly ask the same question
- Episodes last between 1–24 h, but never > 24 h
- Patients are usually disoriented in time and place, but not usually person.
- Normal perception, preserved personal identity
- Absence of other cognitive or neurological impairments.
- Patients have no recall of events after the attack

Investigations

- If the diagnosis is clear, further diagnostic procedures are not necessary.
- If the diagnosis is uncertain:
 - ⇒ MRI: evidence of typical focal, hyperintense lesions in the hippocampus
 - ⇒ EEG: exclude differential diagnoses (e.g., epileptic amnesic attacks)

Differential diagnosis

- Epilepsy can present with discreet episodes of amnesia. This syndrome is called transient epileptic amnesia. Features that suggest epilepsy are:
 - ⇒ shorter duration (should be less than 1 hour)
 - ⇒ multiple attacks
 - ⇒ onset on waking from sleep
 - ⇒ accompanying epileptic features e.g. motor automatism, stereotyped behaviour, limb shaking.

Management

- No treatment is needed except observation until recovery.
- Most patients recover within 24 hours and do not get further such episodes.
- Imaging is considered if amnesia does not resolve after 24 hours.

Transient global amnesia

The best line of management → Admit for observation

Prognosis

- Resolves spontaneously within 24 h
- Recurrence is unusual.

Restless legs syndrome (RLS)

Restless leg syndrome - management includes dopamine agonists such as ropinirole

Definition

 Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia.

Epidemiology

• It is extremely common, affecting between 2-10% of the general population.

Males and females are equally affected and a family history may be present

Pathophysiology

 Studies suggest that abnormal dopamine pathways in the brain and impaired iron homeostasis (leading to iron deficiency in the substantia nigra) are the most prominent pathophysiological mechanisms involved.

Features

- Uncontrollable urge to move legs (akathisia).
 - ⇒ initially occur at night but as condition progresses may occur during the day.
 - ⇒ movements during sleep may be noted by the partner periodic limb movements of sleeps (PLMS)
 - **⇒** Begins and/or worsened with rest
 - ⇒ Typically relieved by movement
- Paraesthesias e.g. 'crawling' or 'throbbing' sensations

Investigations

- Iron studies (best initial test)
- Polysomnogram: quantification of periodic limb movements of sleep (PLMS)

Causes

- Primary (common): idiopathic, but is familial in up to 77% of cases
- Secondary
 - ⇒ Chronic conditions
 - ⇒ **Iron deficiency** with or without anemia, vitamin deficiency
 - ⇒ Drugs : H1 antihistamines, Antidepressants, Dopamine antagonists (neuroleptics, metoclopramide, MDMA), Lithium, Beta blockers
 - ⇒ Pregnancy

A low serum ferritin is most likely to be a cause of secondary restless legs syndrome

Diagnosis criteria

- · Exclude iron deficiency anaemia
- The international restless legs syndrome study group four basic criteria for diagnosing RLS:
 - 1. A desire to move the limbs, often associated with paraesthesias or dysaesthesias
 - Symptoms that are worse or present only during rest and are partially or temporarily relieved by activity
 - 3. Motor restlessness, and
 - 4. Nocturnal worsening of symptoms.

Management

- Lifestyle changes (e.g. avoid stimulants in the evening such as caffeine, tobacco and alcohol), regular daily exercise (but avoid exercising close to bedtime)
- · Simple measures: walking, stretching, massaging affected limbs
- Treat the underline cause: Treat any iron deficiency
- 1st line: pregabalin, gabapentin or dopamine agonist (e.g. ropinirole, pramipexole and rotigotine skin patch)

Essential tremor

Essential tremor is an AD condition that is made worse when arms are outstretched, made better by alcohol and propranolol

Causes

 positive family history (50–70%; autosomal dominant inheritance) or sporadic; benign form

Epidemiology

- · Most common form of tremor
- Bimodal distribution: teens and 6th decade of life (common in elderly patients)

Features

- Mostly bilateral postural tremor with a frequency of 5–10 Hz
- · Postural tremor: worse if arms outstretched
- Localization: hands (~ 90%), head (~ 30%; "yes-yes" or "no-no" motion), voice (~ 15%)
- Most common cause of titubation (head tremor)
- Worse with sustained voluntary movement, stress or anxiety.
- · Improved by alcohol and rest

Diagnostics: usually a clinical diagnosis of exclusion

Consider an essential tremor in a patient presenting with chronic bilateral hand tremors without further neurological deficits and positive family history.

Management

- propranolol is first-line
- · primidone (a barbiturate) is sometimes used
- In drug-resistant cases
 - ⇒ Deep brain stimulation (DBS)
 - ⇒ Thalamotomy

MRCPUK-part-1-January 2019 exam: H/O involuntary movements of the head, worse on movement and during stress and relieved by alcohol and sleep. What is the most likely diagnosis? Essential tremor (Essential tremor is the most common cause of titubation (head tremor).

MRCPUK-part-1-January 2020 exam: H/O tremor of the arms, which is worse when arms are outstretched. His father suffered from a similar complaint. What is the most suitable first-line treatment? Propranolol

Holmes tremor

Holmes tremor → lesion in the red nucleus

Overview

• Holmes tremor or rubral tremor is caused by a lesion in the red nucleus.

Causes

• Previous stroke of the red nucleus (the most common cause), head trauma, and demyelinating diseases.

Pathophysiology

• It is assumed that a double lesion is required to develop HT, including the dopaminergic nigrostriatal system and the cerebello-thalamo-cortical or dentate-rubro-olivary pathways

Features

- Irregular low frequency (< 4.5 Hz) tremor, mostly of the upper extremities and affecting both proximal and distal muscles.
- It presents at rest and is aggravated by positioning and movement (combination of resting, postural and action tremor).
- Signs of ataxia and weakness can occur.

Differential diagnosis: Holmes tremor VS Parkinson

• In contrast to Holmes tremor, Parkinsonian resting tremor (4-6 Hz) improves with voluntary activity and involves distal muscles.

Treatment

- Initial medical therapy: levodopa
- For refractory cases: thalamotomy or chronic thalamic stimulation

Friedreich's ataxia

Friedreich's ataxia: most common cause of death \rightarrow heart failure due to hypertrophic cardiomyopathy

Pathophysiology

- · Autosomal recessive, trinucleotide repeat disorder
- Trinucleotide repeat expansion (of the nucleotide triplet GAA) in the FXN gene on chromosome 9; → deficiency of frataxin (an iron-binding protein) → intramitochondrial accumulation of iron and; mitochondrial dysfunction → oxidative damage and degeneration of CNS and PNS
- Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in not demonstrating the phenomenon of anticipation.

Epidemiology

- The most common early-onset hereditary ataxias.
- Peak incidence: 10-15 years

Features

- Neurological
 - Gait ataxia: due to damage to the spinocerebellar tracts (often a presenting feature)
 - Impaired proprioception and vibration sense due to damage to the dorsal columns
 - Loss of deep tendon reflexes due to degeneration of the dorsal root ganglia
 Absent ankle jerks/extensor plantars
 - ⇒ Spastic paralysis due to degeneration of the lateral corticospinal tract
 - ⇒ Nystagmus, dysarthria and dysphagia
 - ⇒ Sensory-motor peripheral neuropathy
- Other features
 - ⇒ Hypertrophic obstructive cardiomyopathy (90%, most common cause of death)
 - ⇒ **Diabetes mellitus** (10-20%)
 - ⇒ Bilateral pes cavus (high-arched palate)
 - ⇒ Kyphoscoliosis

Diagnosis

- Definitive diagnosis → Genetic testing for expansion of the GAA triplet repeat in the FXN gene
- MRI brain and spinal cord: cervical spine atrophy (minimal cerebellar atrophy)
- Nerve conduction studies
 - ⇒ Sensory: absent or reduced sensory nerve action potentials (SNAP)
 - ⇒ Motor: normal until advanced stages

Friedreich's ataxia VS Ataxic-telangiectasia

Friedreich's ataxia versus Ataxia-telangiectasia			
	Friedreich's ataxia	Ataxia-telangiectasia	
Epidemiology	The most common autosomal recessive ataxia in children	The second most common autosomal recessive ataxia in children, after Friedreich's ataxia	
Affected chromosome	Chromosome 9	Chromosome 11	
Affected gene	FXN gene	ATM gene	
Age of presentation	Late childhood (10-15 years old)	Early childhood (1 – 5 years old)	
Similarities	Autosomal recessive cerebellar ataxia onset in childhood	Autosomal recessive Cerebellar ataxia Onset in childhood	
Associations	Kyphoscoliosis and pes cavus (high- arched palate)	Immunodeficiency & risk of developing malignancy	
Cause of death	Hypertrophic cardiomyopathy (HCM)	Bronchiectasis or malignancy	
Average life expectancy	37 years	25 years	

Ataxic telangiectasia

The 4 A's of ataxia telangiectasia: ATM gene, Ataxia, spider Angiomas, and IgA deficiency.

Overview

- Autosomal recessive disorder
- Caused by a defect in the ATM gene which encodes for DNA repair enzymes.
- It is one of the inherited combined immunodeficiency disorders.
- It typical presents in early childhood with abnormal movements. oculomotor apraxia and choreoathetosis developing later.

Features

- Cerebellar ataxia
- Telangiectasia (spider angiomas)
- IgA deficiency resulting in recurrent chest infections → bronchiectasis
- Increased risk of malignancy (10%), lymphoma or leukaemia, gastric carcinoma

Diagnosis

- Elevated **serum alpha-fetoprotein**, at least two standard deviations above the normal range, is diagnostic of ataxia-telangiectasia
- Confirmed by the identification of mutations on the ATM gene.

Prognosis

• Death in the late teens or 3rd decade from **bronchiectasis** is typical.

Avoid x-ray exposure because of high sensitivity to radiation and increased risk of malignancy.

Sleep

Sleep Stage	Description	EEG Waveform
	Awake and alert	Beta
	Awake and eyes closed	Alpha
Stage N1	Light sleep	Theta
Stage N2	Deeper sleep	Sleep spindles and K complexes
Stage N3	Deepest non-REM sleepSleep walkingNight terrorsBed wetting	• Delta
REM	Dreaming	Beta

• REM Sleep:

- ⇒ Physiology
 - rapid eye movement
 - same EEG pattern as when awake
 - erection
 - ↑ and variable pulse and blood pressure
 - loss of muscle tone

⇒ Timing

- occurs every 90 min
- duration ↑ with every cycle
- amount of REM sleep ↓ with age
- ⇒ Acetylcholine is the principle neurotransmitter
- ⇒ Norepinephrine, serotonin, and histamine suppress REM sleep
 - therefore, certain antidepressants (eg, SSRI, SNRI) can pharmacologically suppress REM sleep

Sleep paralysis

Overview

- Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep.
- It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye
 movement) sleep.
- Mechanism is believed to involve a dysfunction in REM sleep.
- · Males and females are affected equally.

Feature

- · aware but unable to move.
- · may include: hallucinations, fear.
- feeling of suffocation may present (although the respiratory muscles are only ever mildly
 affected in comparison with the limbs).
- · Episodes generally last less than a couple of minutes.

Associations

- May occur in those who are otherwise healthy
- Narcolepsy
- Familial
- Can be triggered by sleep deprivation, psychological stress, or abnormal sleep cycles

Treatment

- · reassured that the condition is common and not serious.
- Other options that may be tried including sleep hygiene, cognitive behavioral therapy, and antidepressants.
- · if troublesome clonazepam may be used

Narcolepsy

Definition

Daily periods of excessive daytime sleepiness for ≥ 3 months

Pathophysiology

- Narcolepsy type 1: Loss of lateral hypothalamic neurons, which produce hypocretin-1 and hypocretin-2 (i.e. orexin A and orexin B) → severe hypocretin (orexin) deficiency → dysregulation of sleep-wake cycles
 - ⇒ Orexin (Hypocretin) is a neuropeptide that is released to increase the activity of brain regions involved in wakefulness, including the raphe nuclei and tuberomammillary nucleus and locus coeruleus.
- Narcolepsy type 2: Idiopathic

Features

- Triad of:
 - 1. Sleep paralysis
 - 2. Excessive daytime somnolence and
 - **3. Cataplexy.** About 5% of patients with narcolepsy have cataplexy.
- Sleep hallucinations
 - ⇒ hypnagogic hallucinations: just before sleep
 - ⇒ hypnopompic hallucinations: just before awakening

Hypnagogic hallucinations occur while going to sleep.

Diagnosis

- Diagnosis is a clinical one, supported by an overnight polysomnogram and multi sleep latency test.
- Lumbar puncture: decreased CSF hypocretin-1 (orexin A) levels due to a loss of orexigenic neurons in the lateral hypothalamus

Treatment

Non-amphetamine-based stimulants, such modafinil, are the treatment of choice.

Cataplexy

- Cataplexy describes the sudden and transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened).
- Features range from buckling knees to collapse.
- Longer episodes can be associated with hallucinations.
- Around two-thirds of patients with narcolepsy have cataplexy.

Head injury

CT head immediately (within the one hour)

- GCS < 13 on initial assessment
- GCS < 15 at 2 hours post-injury
- suspected open or depressed skull fracture.
- any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- · post-traumatic seizure.
- · focal neurological deficit.
- · more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- · age 65 years or older
- · any history of bleeding or clotting disorders
- dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an
 occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5
 stairs)
- more than 30 minutes' retrograde amnesia of events immediately before the head injury
- If a patient is on warfarin perform a CT head scan within 8 hours of the injury regardless of whether he have risk factors for an intracranial injury.

Head injury: types of traumatic brain injury

Type of injury	Notes		
Extradural (epidural) haematoma	 Bleeding into the space between the dura mater and the skull. Often results from acceleration-deceleration trauma or a blow to the side of the head. The majority of epidural haematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery. Features		
	Epidural haematoma - lucid interval		
	 features of raised intracranial pressure lucid interval (apparent recovery from the initial concussion, but deterioration is usually within 15-30 minutes). 		
Subdural haematoma	 Bleeding into the outermost meningeal layer. Most commonly occur around the frontal and parietal lobes. Risk factors include old age, alcoholism and anticoagulation. Slower onset of symptoms than epidural haematoma. 		
Subarachnoid haemorrhage	Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury		

Comparison of Intracranial Haemorrhage

Feature	Subarachnoid	Subdural	Extradural
Location	The inner most layer around the brain tissue	Between the dura mater and arachnoid mater	The outermost layer, between the skull and dura mater
Mechanism	Usually due to rupture of a blood vessel (e.g. berry aneurysm or AVM). Pain typically felt at the back of the head	Usually due to trauma causing damage to one of the <i>bridging veins</i> . Trauma may be minor and could be many months ago. Can be acute or chronic.	Due to direct moderate / severe head trauma. Typically around the eye, causing fracture of the temporal or parietal bone, resulting in laceration of the middle meningeal artery and/or vein
Pain	Sudden onset, painful	Possible dull headache	Likely, and often severe, but not sudden onset
Consciousness	May become impaired quickly – if so, a very bad prognostic indicator	Fluctuates, often over weeks or even months	Classically, an initial lucid period, followed by impaired consciousness
Neurological signs	May be present; are a poor prognostic indicator	Often insidious. May involve memory impairment, epilepsy, drowsiness, dizziness. Often occur weeks / months after injury	Typically after a <i>lucid period,</i> severe headache, impaired consciousness. Vomiting, seizures, drowsiness, confusion, and later, coma.
Investigations	CT – should show irregular shaped bleed. If absent, and still suspicious, do LP to confirm (blood in CSF, CSF turn yellow when left to stand – xanthochromia)	CT / MRI – classically shows a <i>crescent</i> of blood around the brain tissue, and midline shift	CT / MRI – described as a <i>lens</i> Shaped lesion – meaning it is biconvex. LP is contraindicated! X-ray may show skull fracture
Management	If few symptoms, surgical clipping of platinum coiling of aneurysm, or if AVM then balloon therapy and stenting are beneficial. Give <i>Nimodipine</i> to reduce risk of vasospasm (and ↑ survival) as long as BP can be maintained.	Burr hole or craniotomy	Surgery to evacuate blood and ligate bleeding vessels

Which vessel is involved?

subdural haematomas	Bridging veins
subarachnoid haemorrhage	anterior and posterior communicating arteries
extradural haematoma	middle meningeal artery

Acute extradural and subdural haematomas would both be high attenuation and anatomically located next to the skull - extradural haematomas have a convex border whilst subdural haematomas have a concave border.



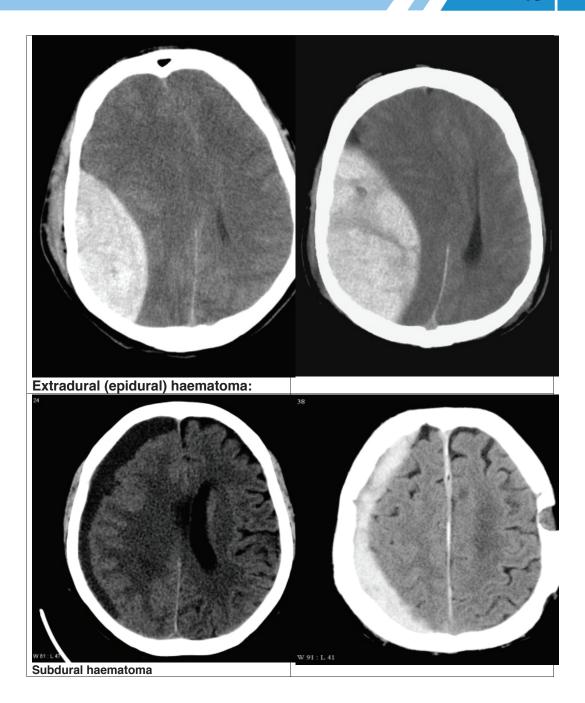
Subarachnoid haemorrhage

CT image shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the inter-hemispheric fissure.

This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.

Post-concussion syndrome : features

- headache and neck discomfort
- changes in memory
- Poor concentration span and Subjects are easily distracted.
- dizziness
- irritability
- · depression or anxiety
- sleep disturbance
- Anxiety is common



Subdural haemorrhage

Fluctuating consciousness = subdural haemorrhage

The history of progressive 'confusion' and unsteadiness for some weeks followed by an acute exacerbation is a typical presentation of a subdural haematoma in the elderly population.

Basics

- most commonly secondary to trauma e.g. old person/alcohol falling over
- initial injury may be minor and is often forgotten
- caused by bleeding from damaged bridging veins between cortex and venous sinuses
- The phrase 'fluctuating conscious level' is common in questions and should always bring to mind subdural haemorrhage
- The combination of falls, alcohol excess, fluctuating episodes of confusion and focal neurology points towards a diagnosis of subdural haemorrhage.

Features

- headache (The most common presenting symptom, seen in up to 80% of patients)
- · classically fluctuating conscious level
- raised ICP → bilateral papilloedema
- Other common symptoms are:
 - ⇒ Fatigue
 - ⇒ memory impairment
 - ⇒ confusion
 - ⇒ nausea and vomiting
 - ⇒ impaired vision
 - ⇒ seizures
 - ⇒ Hemiparesis, or paralysis is also possible.

Treatment

· needs neurosurgical review? burr hole

Acute subdural haematoma

- usually results from acute head trauma
- The haematoma accumulates between the surface of the brain and the dura mater.
- The mortality rate ranges between 50% and 90%.
- A good outcome is most likely if surgical evacuation of the haematoma is prompt and secondary brain injury is prevented.
- Mortality is less likely in:
 - ⇒ younger adults
 - ⇒ patients with a GCS score above 6 or 7
 - ⇒ those with pupil reactivity, and
 - ⇒ those without cerebral contusions or uncontrolled rises in intracranial pressure.

Subarachnoid haemorrhage (SAH)

Overview

Vascular malformations and aneurysms typically bleed in the subarachnoid space.

Causes

- 85% are due to rupture of berry aneurysms
 - ⇒ conditions associated with berry aneurysms include:
 - adult polycystic kidney disease,
 - Ehlers-Danlos syndrome and
 - coarctation of the aorta
 - ⇒ occur most frequently in the anterior half of the circle of Willis.
 - ⇒ The most common site of aneurysm rupture causing SAH is at the junction of the <u>anterior communicating</u> artery and anterior cerebral artery.
- AV malformations
- trauma
- tumours

Features

- headache
 - ⇒ sudden onset.
 - ⇒ typically described as the worst headache experienced.
- · Meningism:
 - ⇒ neck stiffness,
 - ⇒ photophobia,
 - ⇒ nausea and vomiting,
 - ⇒ meningeal stretch signs (e.g., Kernig's sign and Brudzinski's sign)

Hunt and Hess scale: grades SAH: Severity and mortality increase with grade:

- 1. grade-1: Asymptomatic or minimal headache & slight neck stiffness
- 2. grade-2: Moderate or severe headache with neck stiffness, but no neurological deficit other than cranial nerve palsy
- 3. grade-3: Drowsiness with confusion or mild focal neurology
- 4. grade-4: Stupor with moderate to severe hemiparesis or mild decerebrate rigidity
- 5. grade-5: Deeply comatose with severe decerebrate rigidity.

Complications

- rebleeding (in 30%)
- obstructive hydrocephalus (due to blood in ventricles)
- · vasospasm leading to cerebral ischaemia
 - Cerebral ischemia may be delayed as a result of delayed cerebral ischaemia (DCI) or cerebral vasospasm.
 - It is the most common cause of death and disability following aneurysmal (SAH).
 - ⇒ It may lead to death or permanent neurologic deficits in over 17-40% patients following SAH.
 - ⇒ The clinical diagnosis of DCI is made when the patient experiences an altered level of consciousness or a new focal neurologic deficit following an initial bleed.

- ⇒ Typically, the development of DCI starts on day 3 after the initial SAH and is maximal at days 5-14, resolving on day 21.
- ⇒ This can cause serious morbidity or death in up to 30% of patients with SAH.
- ⇒ Treatment for DCI includes prophylactic administration of nimodipine and current neurointensive care.

Investigations

- If SAH is suspected, obtain a head CT without contrast.
- If CT is ⊖, LP is mandatory.
 - Non-contrast CT-scan:
 - the most appropriate initial investigation
 - ⇒ negative in 5%
 - Lumbar puncture (LP):
 - ⇒ done after 12 hrs (allowing time for xanthochromia to develop)
 - (presence of oxidized RBCs)
 - ⇒ (LP) is not usually required unless the history is suggestive, and the CT is normal.
 - CSF examination with <u>spectrophotometry</u> for haemoglobin breakdown products, particularly CSF bilirubin, which proves the presence of prior recent bleeding.
 - This is now recommended instead of measuring the CSF red cell count or xanthochromia, as the procedure of lumbar puncture itself can introduce red cells into the CSF sample and thus give an uninterpretable result.
 - (spectrophotometry remains positive for 2 weeks with 100% sensitivity, sensitivity drops thereafter).
 - CT cerebral angiography
 - ⇒ If CT image shows blood in the subarachnoid space, the most appropriate next investigation is → CT cerebral angiography
 - to look for an underlying aneurysm or vascular malformation which may be amenable to neurosurgical intervention.

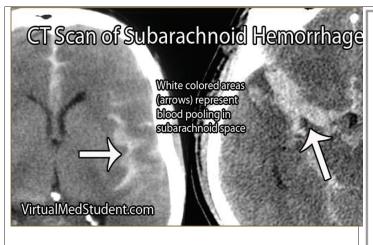
Intracranial hemorrhage ECG changes:

- Deep symmetrical T- wave inversion
- Prolonged QT interval

Management

- Neurosurgical opinion
 - ⇒ no clear evidence over early surgical intervention against delayed intervention
- Nimodipine (a calcium channel blocker)
 - ⇒ SAH → cerebral vasospasm (in 30% of patients) → result in further ischemia due to a reduction in distal blood flow.
 - ⇒ All patients are prescribed a calcium channel blocker (eg Nimodipine) to prophylactically prevent this.
 - ⇒ reduces cerebral vasospasm (hence maintaining cerebral perfusion) → reduce the incidence and severity of neurological deficits.
 - post-operative nimodipine (e.g. 60mg / 4 hrly, if BP allows) has been shown to reduce the severity of neurological deficits but doesn't reduce rebleeding

What is the most appropriate minimum interval between neurological observations in the first instance? Answer \rightarrow 30 min



Conditions
associated with
berry aneurysms
that can MAKE an
SAH more likely:

Marfan's syndrome
Aortic coarctation
Kidney disease
(autosomal
dominant, polycystic)
Ehlers-Danlos syndrome
Sickle cell anemia
Atherosclerosis
History (familial)

Brain stem herniation

The sudden onset of headache, ataxia and vomiting suggest \rightarrow an intracranial haemorrhage, which leads to \rightarrow mass effect and \rightarrow subsequent **brain stem herniation**.

- Brain herniation often causes false localising signs due to compression of various areas of the brain.
- it usually follows two patterns:
 - 1. **uncal herniation**: presented with:
 - third nerve paresis
 - (ipsilateral dilated pupil, abnormal external ocular movements, including nystagmus)
 - The third nerve paresis occurs due to compression of the parasympathetic fibres around the third nerve, which results in unopposed sympathetic response.
 - contralateral hemiparesis
 - which can lead to ipsilateral hemiparesis.
 - Contralateral hemiparesis occurs with compression of the cerebral peduncle.
 - Ipsilateral hemiparesis and third nerve palsy occur late when the lateral translation is so great that it compresses the contralateral third nerve and peduncle.
 - 2. **Central herniation**: presents with:
 - confusion and drowsiness,
 - followed by impaired vertical gaze,
 - small pupils,
 - impaired oculocephalic reflexes
 - Bilateral corticospinal tract signs including increased tone and Babinski signs.

- signs of raised intracranial pressure:
 - bradycardia,
 - hypertension,
 - irregular breathing (Cushing response)
 - and a sixth-nerve palsy.
- The sixth nerve is usually the first to be compressed due to its long extracerebral intracranial course.
- Diplopia from either a third or sixth nerve palsy can cause nystagmus.

Treatment

- ⇒ immediate intensive care support, with intubation and hyperventilation.
- ⇒ The case should be discussed urgently with neurosurgeons, and their advice sought regarding the possibility of operative intervention.
- ⇒ Intravenous mannitol and other hyperosmolar solutions are often indicated, and should be considered.

Brain stem death tests include:

- Pupillary light response CN II and III
- Corneal reflex, response to supraorbital pressure CN V and VII
- Vestibulo-ocular reflex CN III and VIII
- Gag reflex CN IX and X
- Cough reflex CN X
- Absence of respiratory effort.

Encephalitis

Causes

- Direct invasion by a neurotoxic virus (encephalitis).
 - ⇒ most commonly caused by enteral viruses, herpes simplex virus (HSV) 1 and 2, varicella, cytomegalovirus (CMV), and Epstein-Barr virus (EBV).
 - occasionally caused by respiratory viruses, human herpes virus 6 (HHV6), rubella, or mumps.
- Post-infectious encephalopathy: delayed brain swelling because of an immunological response to the antigen, i.e. a neuroimmunological response.
 - ⇒ caused by measles or varicella zoster (cerebellar ataxia).
- Slow virus infection, for example, human immunodeficiency virus (HIV) or subacute sclerosing panencephalitis (SSPE).
- limbic encephalitis
 - ⇒ In 60% of cases, limbic encephalitis is a paraneoplastic disorder and indicates the presence of an underlying cancer; the most common underlying malignancy is small cell lung carcinoma (SCLC), followed by testicular cancer, thymoma, and Hodgkin's lymphoma.
 - Among patients with SCLC, the anti-Hu antibody is present in about 50% of those with predominant or isolated symptoms of limbic encephalitis
 - ⇒ In contrast to patients with other paraneoplastic neurologic syndromes, in whom magnetic resonance imaging (MRI) is of limited usefulness in helping to establish the diagnosis, patients with limbic encephalitis may present with early MRI changes suggestive of the disorder.5
 - Typically, the MRI shows hyperintense abnormalities in the medial aspect of the temporal lobes.6
 - These MRI abnormalities should be differentiated from those in patients with herpes simplex encephalitis, in whom the MRI usually shows signs of

oedema, mass effect, contrast enhancement, and, sometimes, areas of haemorrhage.

Differential diagnosis of acute/subacute encephalopathy is etiologically wide and includes:

- Neurodegenerative (for example sporadic Creutzfeldt-Jakob disease [CJD])
- Endocrine (hypothyroidism)
- Toxicological (lead, arsenic poisoning)
- Nutritional (vitamin B1 deficiency)
- Infective (HSV, HIV), and
- · Autoimmune causes.

Paraneoplastic neurological syndromes

- uncommon but important because they <u>frequently present before the malignancy</u>, and because they cause severe neurological disability.
 - **⇒** Limbic encephalitis
 - ⇒ Cerebellar degeneration
 - ⇒ Opsoclonus-myoclonus
 - ⇒ Sensory neuronopathy
 - ⇒ Lambert-Eaton myasthenic syndrome
 - ⇒ Myasthenia gravis
 - ⇒ Dermatomyositis, and
 - ⇒ Polymyositis.
- Most paraneoplastic syndromes respond poorly to immunomodulatory treatment although occasional improvement is seen when the underlying tumour is treated.

Herpes simplex encephalitis (HSE)

HSE: behavioral changes and CT head showing temporal lobe changes

Overview

- Herpes simplex (HSV) encephalitis is a common topic in the exam.
- The virus characteristically affects the temporal lobes questions may give the result of imaging or describe **temporal lobe signs** e.g. aphasia.
- Temporal lobe involvement is common (limbic encephalitis), in particular the anterior temporal lobes. These abnormalities are visible on CT or MRI.
- Winter is the peak incidence.
- It has peaks of presentation in the young and old.

Types

- Both herpes simplex virus type 1 and type 2 can cause encephalitis:
 - ⇒ Herpes simplex type 1 is the virus associated with encephalitis in older children and adults.
 - HSV-1 responsible for 95% of cases in adults
 - typically affects temporal and inferior frontal lobes
 - ⇒ **Herpes simplex type 2** is characterised by generalised brain involvement, but is almost exclusively seen in neonates who acquire the virus during delivery.

Herpes simplex encephalitis presents with:

- Behavioural changes or psychiatric disturbance
- Focal seizures
- Fever and
- · Alteration in consciousness.

Features

- fever, headache, psychiatric symptoms, seizures, vomiting
- · focal features e.g. aphasia
- peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis

Investigation

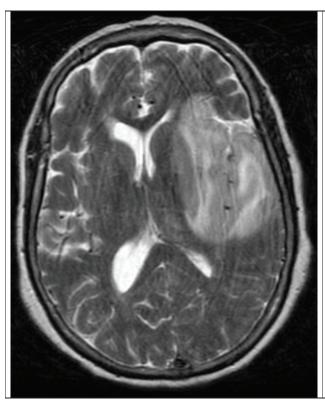
- CSF: lymphocytosis, elevated protein, mildly raised red cells and a normal or low glucose.
- PCR for HSV on (CSF) is a highly specific test.
- MRI brain is the investigation of choice initially, which should demonstrate temporal lobe changes, although often CT only is available out of hours.
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) normal in one-third of patients
 - ⇒ CT scan of the brain may be normal, but MRI may reveal the diagnosis.
- EEG pattern: lateralised periodic discharges at 2 Hz

Treatment

- · intravenous aciclovir
 - ⇒ Immediate treatment is required on clinical suspicion do not wait
 - ⇒ continued until CSF PCR is negative, or for at least 14 days.
 - □ Intravenous fluids and aciclovir is the best option here.

Prognosis

- The prognosis is dependent on whether aciclovir is commenced early.
 - ⇒ If treatment is started promptly the mortality is 10-20%.
 - ⇒ Left untreated the mortality approaches 80%



MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

MRCPUK-part-1-January 2012: H/O Confusion, headache and fever + seizure. MRI shows patchy haemorrhagic changes in the temporal lobe. Given the likely diagnosis, what is the treatment of choice?

→ Supportive treatment + intravenous acyclovir. (△ Herpes simplex encephalitis)

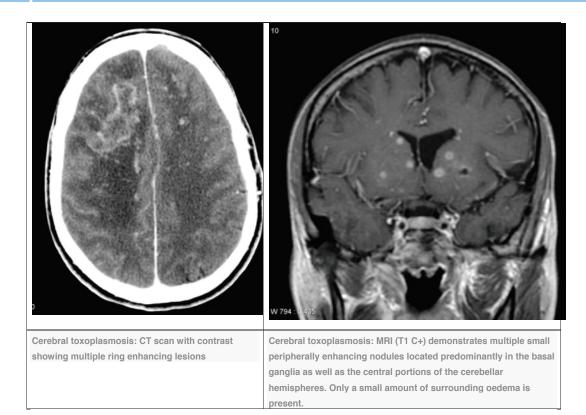
HIV: neurocomplications

Focal neurological lesions

<u>Toxoplasmosis</u>

HIV - multiple ring enhancing lesions = toxoplasmosis

- the **most common** neurological infection seen in HIV,
- occurring in up to 10% of patients
- accounts for around 50% of cerebral lesions in patients with HIV
- occurring at CD4 counts of less than 100 cells/mm³.
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



The differential diagnosis of ring-enhancing lesions on CT in a patient with AIDS include:

- Cerebral toxoplasmosis
- Abscesses
- Metastases
- Atypical CNS lymphoma.

Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- · associated with the Epstein-Barr virus
- · CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

Differentiating between toxoplasmosis and lymphoma is a common clinical scenario in HIV patients. The table below gives some general differences.

Condition	CT finding
Toxoplasmosis	 Multiple lesions
	Ring or nodular enhancement
	Thallium SPECT negative
Lymphoma	Single lesion
	Solid (homogenous) enhancement
	 Thallium SPECT positive
Tuberculosis	single enhancing lesion
Encephalitis	oedematous brain
Cryptococcus	meningeal enhancement, cerebral oedema
Progressive multifocal leukoencephalopathy	single or multiple lesions,
(PML)	no mass effect,
	don't usually enhance
AIDS dementia complex	cortical and subcortical atrophy

Given the more limited availability of SPECT compared to CT many patients are treated empirically on the basis of **scoring systems**, for example there is a 90% likelihood of toxoplasmosis if all of the following criteria are met:

- toxoplasmosis IgG in the serum
- CD4 < 100 and not receiving prophylaxis for toxoplasmosis

multiple ring enhancing lesions on CT or MRI

Tuberculosis

- · much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

Generalised neurological disease

Encephalitis

- · may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

Cryptococcus

- most common fungal infection of CNS
- typically there is a sub-acute onset of symptoms and the disease is associated with raised intracranial pressure (leading to the papiloedema and the falsely localising 6th nerve palsy).
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- · CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion
- raised intracranial pressure (ICP) is thought to be caused by the yeast cells and fungal polysaccharides forming microscopic plugs and blocking CSF resorption in the subarachnoid villi.
- management
 - ⇒ The best management would be intravenous anti-fungal agents, such as amphotericin B and flucytosine.
 - ⇒ Therapeutic lumber puncture is also advocated to reduce ICP.
 - Anti-retroviral (ARV) therapy should not be started immediately, as there is a very high risk of the patient developing IRIS (immune reconstitution inflammatory syndrome). Instead, ARVs should be delayed for several weeks or months after initiating treatment.

Progressive multifocal leukoencephalopathy (PML)

Overview

- widespread demyelination
- rare and fatal opportunistic infection of the central nervous system caused by (JC) virus.
 - ⇒ (JC) virus is a papovavirus (polyoma DNA virus) found latent in most healthy adults.

Risk factors

- seen in advanced HIV/AIDS
 - ⇒ With CD4 counts of less than 100 this virus becomes active leading to progressive neurological deterioration.
- Natalizumab has a black-box warning of increased risk of developing (PML),
- Three risk factors have been clearly identified in <u>patients with multiple sclerosis</u> which predispose them to the future developing PML:
 - 1. positive anti-JC viral serum antibodies,
 - 2. prior use of immunosuppressants, and
 - increased duration of natalizumab treatment and its number of infusions (25-49 infusions).

Features

- subacute onset:
- Behavioural changes, speech, motor, visual impairment
- Ataxia
- Head tremor
- Focal neurology progressing over a period of months to paresis and even coma.

Diagnosis

- CT: single or multiple lesions, no mass effect, don't usually enhance.
- MRI is better high-signal demyelinating white matter lesions are seen
- It can be diagnosed via CSF PCR for the JC virus.
- Brain biopsy
 - **⇒** the definitive diagnostic test
 - ⇒ (showing asymmetric foci of demyelination and intranuclear inclusions containing the JC virus).

Treatment

 There is no effective treatment, but progression can be slowed by initiation of antiretroviral therapy.

AIDS dementia complex

- · caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy
- progresses over a longer time period than progressive multifocal leukoencephalopathy (PML).
- Differential diagnosis
 - ⇒ Patients with cryptococcal meningitis present with headache, fever, vomiting and few neurological signs.
 - ⇒ PML can present at any CD4 count with ataxia, behavioural changes and focal neurological signs, often progressing over a period of months to paresis or even coma
 - ⇒ **Toxoplasmosis** presents with headache, fever and seizures. It has a typical CT head scan with ring enhancing lesions.

January 2019 exam: H/O HIV positive, admitted following a seizure + headaches, night sweats and poor appetite. CD4=89 u/l. CT head =Single homogenously-enhancing lesion in the right parietal lobe. What is the most likely diagnosis?

→ Primary CNS lymphoma

January 2016 exam: HIV positive, admitted with confusion, drowsiness and headache. temperature is 37.2°C. CT brain (with contrast): Multiple hypodense regions predominantly in the basal ganglia which show ring enhancement. Minimal surrounding oedema. No mass effect. What is the most likely diagnosis?

→ Cerebral toxoplasmosis (HIV - multiple ring enhancing lesions = toxoplasmosis)

Motor neuron disease (MND)

Progressive motor weakness and pseudo-bulbar palsy + normal sensations + normal brain imaging \rightarrow always think of amyotrophic lateral sclerosis.

Electromyography is the best investigation to carry out next.

Overview

The primary defect is in the anterior horn cells

Epidemiology

- Sex: ♂ > ♀
- · Rarely presents before 40 years

Types

- 1. Amyotrophic lateral sclerosis (50% of patients)
 - ⇒ Lower motor neuron (LMN) signs in arms and upper motor neuron (UMN) in legs
 - anterior motor horn degeneration leads to lower motor neuron signs.
 - lateral corticospinal tract degeneration leads to upper motor neuron signs.
 - ⇒ Causes
 - un known in 90 % (sporadic)
 - inherited (10%)
 - polygenic inheritance
 - A defect on chromosome 21, which codes for superoxide dismutase 1 (SOD1), is associated with about 20% of familial cases of ALS, or about 2% of ALS cases overall.
- 2. Primary lateral sclerosis
 - ⇒ UMN signs only
- 3. Progressive muscular atrophy
 - □ LMN signs only
 - ⇒ affects **distal** muscles before proximal
 - ⇒ carries best prognosis
- 4. Progressive bulbar palsy
 - ⇒ Accounts for ~ 0.2% of all motor neuron diseases
 - ⇒ Age: 75–80 years
 - palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
 - ⇒ carries worst prognosis
 - ⇒ Most common cause of death is respiratory complications secondary to recurrent aspiration(e.g., pneumonia).

Features

- Clues, which point towards a diagnosis of motor neuron disease:

 - ⇒ Absence of sensory signs/symptoms
 - ⇒ Lower motor neuron signs in arms and upper motor neuron signs in legs
 - ⇒ Wasting of the small hand muscles/tibialis anterior is common

Other features

- ⇒ Asymmetric limb weakness
- ⇒ Dysarthria, dysphagia, and tongue atrophy
- ⇒ 20% of patients present with bulbar onset (late feature and suggests a poor prognosis).
- ⇒ Pseudobulbar palsy
- → Onuf nucleus (of spinal cord segments S1-S4) is preserved, thus the bladder and rectal sphincters remain normal through the course of the disease.
- ⇒ Abdominal reflexes are usually preserved and sphincter dysfunction if present is a
 late feature
- ⇒ Fronto-temporal dementia (10 %)
- ⇒ **Respiratory involvement** (present in up to **50% of MND** cases at presentation).
 - Bilateral diaphragmatic weakness causing orthopnea and exertional dyspnoea
 - Respiratory failure is the commonest cause of death in this condition.

Features <u>NOT</u> compatible with MND

- ⇒ Sensory impairment . Note it may be present due to concomitant <u>diabetic</u> peripheral neuropathy.
- ⇒ Optic atrophy
- ⇒ External ocular muscles palsy
- ⇒ Cerebellar signs
- ⇒ Bladder dysfunction.

Diagnosis

- **Electromyography** shows: Denervation: indicated, e.g., by fibrillations
 - ⇒ reduced number of action potentials
 - ⇒ increased amplitude.
- Nerve conduction studies: usually normal, to exclude a neuropathy.
- MRI: to exclude the differential diagnosis of cervical cord compression and myelopathy
- Creatine kinase → increased
- Nerve conduction studies: usually normal

Management

Motor neuron disease - treatment: NIV is better than riluzole

Motor neuron disease - riluzole

- Riluzole (glutamate antagonist)
 - prevents stimulation of glutamate receptors → decreasing
 presynaptic glutamate release (thereby limiting cytotoxic effects of this neurotransmitter)
 - ⇒ prolongs life by about 3 months
 - ⇒ Common side effects: nausea, asthenia, abdominal pain, dizziness, asymptomatic elevation in liver enzymes.
 - ⇒ Rare life-threatening side effects: pancreatitis, hepatitis, and neutropenia

- Respiratory care
 - ⇒ Non-Invasive Ventilation (NIV) (usually BIPAP) is used at night
 - have the greatest effect on survival → survival benefit of around 7 months
- Radiologically inserted gastrostomy feeding (in case of dysphagia)

Prognosis

- Poor: Median survival time from onset of symptoms is three to five years.
- Poor prognostic factors include: low forced vital capacity (FVC) and older age.

Bulbar VS Pseudobulbar palsy

Comparison of bulbar and pseudobulbar palsy

Pseudobulbar Palsy	Bulbar Palsy
 Bilateral damage or injury of corticobulbar tracts to nerve nuclei of cranial nerves V, VII, IX, X, XI, and XII Upper motor neuron palsy of the respective muscles 	 Bilateral damage or injury of the nerve nuclei of cranial nerves IX, X, XI, and XII Lower motor neuron palsy of the respective muscles
Lower motor neurone signs absent	Lower motor neurone signs present
Spastic tongue (no wasting/fasciculations)	Wasted tongue, fasciculations
Spastic dysarthria	Nasal speech
Labile emotions	Normal emotions
Facial expressions: absent	Facial expression: normal
Gag reflex: brisk (exaggerated)	Gag reflex: absent
Jaw jerk: exaggerated	Jaw jerk: normal

Multiple sclerosis (MS)

Multiple sclerosis diagnosis that requires demyelinating lesions that are separated in space and time

Definition

 Demyelinating CNS condition clinically defined by 2 episodes of neurological dysfunction (brain, spinal cord, or optic nerves) that are separated in space and time.

Pathophysiology |

- Pathophysiology of MS is characterized by autoimmune inflammation, demyelination, and axonal degeneration.
- Exact cause remains unknown
- Most commonly accepted theory: Activation of autoreactive T-lymphocytes → inflammatory processes → focal demyelination with partial preservation of axons (acute plaques) → loss of axons and atrophy of oligodendrocytes (chronic plagues) → gliosis → inadequate remvelination
- Genetic susceptibility → Associated with HLA-DR2
- Environmental risk factors → Low vitamin D levels, smoking, EBV, HHV 6
- Most common sites of demyelination in MS

- ⇒ Periventricular areas
- ⇒ Brainstem
- □ Cerebellum
- ⇒ Spinal cord

Epidemiology

- Sex: 9 > 3 (2:1) (MS is more common in women)
- Age of onset: 20-40 years of age
- Ethnicity: ↑ prevalence among the white population

Classification and clinical course

- Relapsing–remitting MS (90%, the most common clinical course)
 - ⇒ Lesions developed at different times and in different anatomical locations
 - ⇒ Symptoms remit almost completely between exacerbations
- Primary progressive MS (10%):
 - ⇒ Progressive neurological deterioration over 1 year or more
 - ⇒ Continuous worsening of symptoms from the first onset of the disease
- Secondary progressive MS: Continuous worsening of symptoms in between exacerbations

Features

- Non-specific features: eg: lethargy (75%).
- Optic neuritis
 - **⇒** Most often the earliest manifestation
 - ⇒ Typically unilateral
 - ⇒ Can be painful
 - ⇒ Impaired vision and color blindness
 - ⇒ Relative afferent pupillary defect (Marcus Gunn pupil)
 - ⇒ Any patient with isolated optic neuritis → refer to a neurologist for further assessment
 - ⇒ The cumulative probability of developing MS by 15 years after onset of optic neuritis is 50%
- Internuclear ophthalmoplegia (INO)
 - ⇒ Result from a lesion in the medial longitudinal fasciculus (MLF)
 - ⇒ Ipsilateral medial rectus weakness but an intact convergence reflex
 - ⇒ Disconjugate, lateral gaze nystagmus in the contralateral eye
 - ⇒ More frequently bilateral than unilateral
- Demyelination of spinal cord tracts
 - ⇒ **Lhermitte sign:** a shooting electric sensation that travels down the spine upon flexion of the neck
 - ⇒ Pyramidal tract lesion: **upper motor neuron** weakness (spasticity, hyperreflexia, positive Babinski sign)
 - ⇒ Involvement of the dorsal spinal column
 - Loss of vibration and fine-touch sensation
 - Numbness, paresthesias
 - Sensory ataxia usually involving the trunk or one or more limbs
 - ⇒ Neuropathic pain
- Cerebellar involvement: Charcot neurological triad
 - ⇒ Scanning speech
 - ⇒ Nystagmus
 - ⇒ Intention tremors

- Cranial nerve palsies (diplopia, trigeminal sensory neuralgia, facial palsy)
- Autonomic dysfunction (bowel and bladder neurogenic disorders, impaired sexual function)
- Uhthoff's phenomenon: a reversible exacerbation of neurological symptoms following an
 increase in body temperature, e.g., physical exertion, a warm bath, or fever (worsening of
 vision following rise in body temperature)

Uhthoff phenomenon triggered by a viral infection may mimic an exacerbation of MS.

Fundoscopy is normal in 60% of cases of optic neuritis. Neither the patient nor the doctor are able to see anything.

Multiple sclerosis (MS): presentation

- Loss or reduction of vision in 1 eye with painful eye movements
- Double vision
- Ascending sensory disturbance and/or weakness
- Problems with balance, unsteadiness or clumsiness
- Altered sensation travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's symptom).

Investigations

- Plain MRI (brain and spine): investigation of choice
 - Multiple sclerotic plaques (most commonly seen in periventricular white matter); related to demyelination and reactive gliosis
 - ⇒ Contrast MRI (with gadolinium): enhancement of active lesion during and up to 6 weeks after the exacerbation
- Visual evoked potentials (VEPs)
 - ➡ Highly sensitive for detecting demyelination of the optic nerve and central visual pathways
 - ⇒ May demonstrate abnormality when the MRI is normal, because the optic nerves are often involved early and may be asymptomatic
- Lumbar puncture
 - ⇒ Lymphocytic pleocytosis
 - ⇒ Oligoclonal bands (↑ production of IgG subfractions): the presence of multiple oligoclonal bands in CSF and their absence in the blood is highly suggestive of MS.
 - The appearance of oligoclonal bands in the early stages of the disease indicates a poor prognosis
 - ⇒ ↑ myelin basic protein

Diagnostic criteria (Revised McDonald criteria 2017): used to diagnose MS based on the dissemination of the CNS lesions in **time** and **space**.

- **Dissemination in time (DIT):** appearance of new lesions over time
 - ⇒ Criterion met (≥ 2 exacerbations) occurring at least 30 days apart
 - ⇒ Criterion not met (1 exacerbation) → diagnosis requires confirmation of DIT by one of the following:
 - An additional exacerbation

- MRI that demonstrates the presence of both gadolinium-enhancing and nonenhancing lesions at any time or a new hyperintense T2 or enhancing lesion on follow-up MRI
- Oligoclonal bands in the CSF
- Dissemination in space (DIS) on MRI: presence of lesions in different regions of the CNS
 - ⇒ Criterion met (≥ 2 lesions with objective clinical evidence) of the 4 MS-typical regions of CNS (periventricular, juxtacortical, infratentorial, or spinal cord).
 - ⇒ Criterion not met (1 lesion with objective clinical evidence) → diagnosis requires confirmation of DIS by one of the following:
 - An additional exacerbation with presence of one more lesion with objective clinical evidence involving a different CNS region
 - Presence on MRI of ≥ 1 T2-hyperintense lesion in at least 2 of the following regions: periventricular, juxtacortical, infratentorial, spinal

If the MRI of the brain is inconclusive, what is the most appropriate next investigation? MRI spinal cord

- Small ischaemic lesions in the brain may be difficult to distinguish from demyelination.
- Spinal cord lesions is more specific than brain for inflammatory disorders such as MS rather than ischaemic lesions. Thus, cord imaging is useful when there is diagnostic difficulty.

Management

- Treatment of acute exacerbations
 - ⇒ First line: high-dose glucocorticoid therapy for 3–5 days
 - Oral methylprednisolone 0.5 g daily for 5 days (If not admitted to hospital)
 - IV methylprednisolone 1 g daily for 3–5 days (if oral steroids have failed or not tolerated or need admission to hospital)
 - Steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)
 - ⇒ Second line: plasmapheresis
- **Disease-modifying MS therapy** (prevention of future attacks)
 - ⇒ Beta-interferon
 - Action: Suppresses T cell activity → ↓ proinflammatory cytokines and ↓
 lymphocyte invasion of the CNS
 - Indication: Criteria from the Association of British Neurologists (ABN) for commencing beta-interferon therapy:
 - 1. Has had more than two separate episodes within the last two years
 - 2. Is more than 18-years-old, and
 - 3. Can walk more than 100 metres.
 - Benefits: Reduces number of relapses by one third (30%) and MRI changes, however, doesn't reduce overall disability
 - When to stop it?: Stop beta interferon if three or more relapses occurred per year (as the objective behind using them is to reduce relapse frequency).
 - Side effects
 - Flu-like symptoms
 - Liver dysfunction
 - Thrombotic microangiopathy

- Depression
- Risk of thyroid disease (both, hyper- and hypothyroidism) during the first year only, Keep thyroid function tests under review
- Contraindications
 - History of severe clinical depression
 - Uncontrolled epilepsy
 - Hepatic dysfunction
 - Myelosuppression.
- ⇒ Glatiramer acetate:
 - Action:
 - Immunomodulating drug, acts as a decoy for T cells instead of neuronal myelin
 - Decreases activity of proinflammatory Th1 lymphocytes
 - Safe in pregnancy
 - Save in liver dysfunction
 - Side effects: Chest pain, Lipoatrophy
- ⇒ Natalizumab:
 - Action: An antibody against Alpha-4 Beta-1-integrin (decreases lymphocyte invasion of the CNS) → inhibits the migration of leucocytes into the CNS, hence reducing inflammation and demyelination.
 - Side effects: Risk of progressive multifocal leukoencephalopathy (PML) in patients with (latent) JC virus infection
 - MRI scan is recommended before starting treatment
 - Testing for serum anti-JCV antibodies before starting natalizumab is recommended and should be repeated every 6 months.
 - Commenced as monthly IV infusions
- - Action: Anti-CD52 antibody.
 - Side effects: Secondary, B-cell mediated autoimmune phenomena (e.g., formation of autoantibodies, ITP, glomerulonephritis)
- ⇒ Ocrelizumab
 - Action: An antibody against CD20 that depletes premature and mature Bcells.
 - Side effects:
 - Hepatitis B virus reactivation
 - Immune suppression
- ⇒ Fingolimod:
 - Action:
 - sphingosine-1-phosphate analog that decreases lymphocyte invasion of the CNS (sphingosine 1-phosphate receptor modulator)
 - prevents lymphocytes from leaving lymph nodes. It is an immunomodulator, which sequesters lymphocytes in lymph nodes.
 - Reduce the rate of relapses in relapsing-remitting MS by over half.
 - Side effects
 - increased incidence of varicella zoster, tumour formation and progressive multifocal leukoencephalopathy (PML)
 - Reserved for patients who fail 1st line therapies.
 - An oral formulation is available

Symptomatic treatments

- ⇒ **Spasticity** → **Baclofen** and gabapentin are first-line.
- ⇒ Oscillopsia (loss of natural image stabilization)
 - Consider gabapentin as a first-line
 - Consider memantine as the second-line

⇒ Bladder dysfunction

- May take the form of urgency, incontinence, overflow etc
- Guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
 - ❖ if significant residual volume → intermittent self-catheterisation
 - ❖ if no significant residual volume → anticholinergics may improve urinary frequency

⇒ MS-related fatigue

- Usually described as physical exhaustion that is unrelated to the amount of activity performed.
- Seen in 78% of patients.
- Often aggravated by heat and humidity.
- Offer amantadine to treat fatigue in people with MS.
- Consider mindfulness-based training, cognitive behavioural therapy
- Exercises including yoga may be helpful.

Multiple sclerosis in pregnancy

Only glatiramer acetate is thought to be safe in pregnancy.

Modifiable risk factors for relapse or progression of MS

- Exercise may have beneficial effects on MS
- Live vaccinations may be contraindicated in people with MS who are being treated with disease- modifying therapies.
- Flu-vaccination: possible benefits and possible risk of relapse after flu vaccination.
- Pregnancy
 - ⇒ Decreased relapse rate of MS during pregnancy
 - ⇒ Increased relapse rate in the postpartum period (3–6 months after childbirth)
 - ⇒ The long-term clinical course of MS remains unchanged.

Prognostic features

- Good prognosis features
 - ⇒ female sex
 - ⇒ young age of onset
 - ⇒ relapsing-remitting disease
 - ⇒ sensory symptoms
 - ⇒ long interval between first two relapses
- Ways of remembering prognostic features
 - ⇒ the typical patient carries a better prognosis than an atypical presentation

The episode of poor co-ordination followed a few months later by unilateral optic neuritis raises the possibility of a demyelinating disease. An MRI and LP are next steps confirming the diagnosis.

Internuclear ophthalmoplegia (INO)

Internuclear ophthalmoplegia (INO)

- Impaired adduction of the eye ipsilateral to the lesion and Nystagmus on the Opposite side.
- When covering one eye, unilateral movements will be normal. But when together, the adducting eye will not move past the midline.

Definition

- Damage to the medial longitudinal fasciculus (the connection between the abducens nucleus, CN VI, on one side and the oculomotor nucleus, CN III, on the other), which leads to impaired lateral gaze.
- Manifests primarily with impaired adduction of the eye ipsilateral to the lesion (ipsilateral to the medial longitudinal fasciculus lesion)

Causes

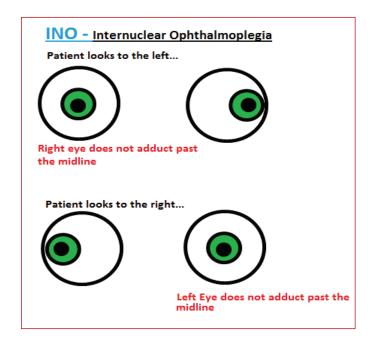
- Multiple sclerosis (MS): characteristic of MS, typically bilateral
- Tumour of the brainstem (eg: glioma)
- Brainstem vascular lesions
- Wernicke's encephalopathy.

Pathophysiology

- Normally, CN VI receives a signal from the ipsilateral paramedian pontine reticular formation and sends a signal to the contralateral CN III via the medial longitudinal fasciculus.
- Activation of the CN VI ipsilateral to the lesion → activation of the ipsilateral lateral rectus →
 abduction of the ipsilateral eye
- Activation of the CN III contralateral to the lesion → activation of the contralateral medial rectus → adduction of the contralateral eye
- Disruption of the medial longitudinal fasciculus fibers linking the CN VI ipsilateral and the
 CN III contralateral to the lesion → failure of signal transmission from CN VI to CN III → the
 ipsilateral lateral rectus is activated while the contralateral medial rectus is not → abduction
 of the ipsilateral eye, no adduction of contralateral eye
- Firing from CN VI which fails to be transmitted to CN III is instead partially transmitted to the lateral rectus ipsilateral to the lesion → nystagmus of the ipsilateral abducting eye

Clinical findings

- Adduction limited in horizontal eye movements
- Adduction is retained in convergence reaction
- The patient may complain of horizontal diplopia.
- Dissociated nystagmus: gaze to the opposite side → nystagmus of the abducted contralateral eye



Chronic progressive external ophthalmoplegia (CPEO)

Overview

- Patients with CPEO typically develop a slowly progressive paresis of extraocular muscles along with bilateral ptosis in the fourth decade of life
- Often associated with mitochondrial disease (inherited only from the mother)
- Most common manifestation of mitochondrial myopathy (in two-thirds of all cases).

Diagnosis

- † Lactate in serum and cerebrospinal fluid
- Muscle biopsy
 → accumulation of enlarged mitochondria "red ragged fibers"
- PCR → mutation of mitochondrial DNA.

Differential diagnosis

- Other causes external ophthalmoplegia must be ruled out, like Graves' disease, myasthenia gravis and glioma
- Kearns-Sayre syndrome: combination of CPEO with pigmentary retinopathy and onset before age 20 (Ophthalmoplegia + retinitis pigmentosa + AV block)

Treatments

• no specific treatment currently, surgery can be used to correct ptosis

Ptosis, Miosis and Mydriasis

Ptosis + dilated pupil → Third nerve palsy

Ptosis + constricted pupil → Horner's

Ptosis

- · Causes of bilateral ptosis:
 - ⇒ Myotonic dystrophy
 - ⇒ Myasthenia gravis (ptosis is much less common in Lambert-Eaton syndrome than myasthenia gravis)
 - ⇒ Syphilis
 - ⇒ Congenital
- Causes of unilateral ptosis, as above plus:
 - ⇒ Third nerve palsy
 - ⇒ Horner's

Miosis

- · Causes of miosis (small pupil)
 - ⇒ Horner's syndrome
 - ⇒ Argyll-Robertson pupil
 - ⇒ senile miosis
 - ⇒ pontine haemorrhage
 - ⇒ congenital
 - ⇒ Drugs causes
 - Opiates
 - parasympathomimetics: pilocarpine
 - organophosphate toxicity

Mydriasis

- Causes of dilated pupils include:
 - ⇒ Holmes-Adie (myotonic) pupil
 - ⇒ Third nerve palsy
 - ⇒ Drugs, and Poisons (atropine, CO, ethylene glycol).

Horner's syndrome

Horner's syndrome: triad of ptosis, miosis and anhydrosis

Horner's syndrome: anhydrosis determines site of lesion:

- Head, arm, trunk → central lesion : stroke, syringomyelia
- Just face → pre-ganglionic lesion : Pancoast, cervical rib
- Absent → post-ganglionic lesion : carotid artery

Overview

- Horner's syndrome develops following disruption of the sympathetic chain.
- Sweat glands are controlled by the sympathetic nervous system, for example, anhydrosis in Horner's syndrome.

Features

- · Miosis (small pupil)
- Ptosis
- Anhydrosis (loss of sweating one side)
- Enophthalmos (sunken eye): in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos
- Facial flushing due to vasodilatation

Types: there are three separate forms of Horner's syndrome, depending on what level the sympathetic fibres are affected at:

First-order sympathetic fibres

- ⇒ Originate in the <u>hypothalamus</u> and descend through the brainstem to their synapse with the preganglionic sympathetic fibres at <u>C8-T2</u>.
- ⇒ Caused by: strokes, multiple sclerosis and basal meningitis.

• Second-order (preganglionic) fibres

- ⇒ Leave the cord at <u>T1</u> and ascend in the sympathetic chain over the lung apex. They synapse in the superior cervical ganglion at the level of <u>C3-C4</u>, at the bifurcation of the common carotid artery.
- ⇒ Caused by: apical lung tumours, lymphadenopathy and lower brachial plexus trauma.

• Third-order (postganglionic) fibres

- ⇒ Pass along the internal carotid artery, with branches passing to the blood vessels and sweat glands of the face. They pass through the cavernous sinus and superior orbital fissure, where they joint the long ciliary nerves to supply the iris dilator and Muller's muscle.
- ⇒ Caused by: **internal carotid artery dissection** or herpes zoster infection.

Because the sympathetic plexus accompanying the internal carotid artery innervates sweat glands only to the medial forehead, facial anhydrosis is only partial when Horner's syndrome is caused postganglionic lesions.

Distinguishing between causes

- Heterochromia (difference in iris colour) is seen in congenital Horner's
- Anhydrosis: see the table below

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhydrosis of the face, arm and trunk	Anhydrosis of the face	No anhydrosis
 Stroke Syringomyelia Multiple sclerosis Tumour Encephalitis 	 Pancoast's tumour Thyroidectomy Trauma Cervical rib 	 Carotid artery dissection Carotid aneurysm Cavernous sinus thrombosis Cluster headache

Orbital apex syndrome

- The combination of optic neuropathy, proptosis, chemosis, Horner syndrome, ophthalmoplegia and involvement of the first branch of the trigeminal nerve is typical of orbital apex syndrome
- The presence of proptosis, with swelling of eyelids and chemosis (swelling of the ocular surface membranes), indicates significant mass extension within the orbit
- The orbital apex syndrome (involvement of cranial nerves II, III, IV and V1) is a superior orbital fissure syndrome with loss of vision

Myasthenia gravis (MG)

Overview

- Myasthenia gravis is an autoimmune disorder caused by autoantibodies directed against acetylcholine receptors (AChR).
- More common in women (2:1)
- Associated conditions
 - ⇒ Other autoimmune diseases: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
 - ⇒ Thymic hyperplasia (50-70%)
 - ⇒ Thymoma (15%)

Feature

- Extraocular muscle weakness: Ptosis, Diplopia, Blurred vision (most common initial symptom)
- Bulbar muscle weakness
 - ⇒ Slurred speech
 - ⇒ Difficulty chewing and/or swallowing: (dysphagia that is worse with liquids than solids in contrast to achalasia which typically affects solids more than liquids, or solids and liquids equally)
- Muscle fatigability (the key feature)
 - Symptoms worsen with increased muscle use throughout the day and improve with rest.
- Proximal muscle weakness
 - ⇒ Rising from a chair

 - ⇒ Brushing hair
 - ⇒ Deep tendon reflexes are not affected.
- Respiratory muscle weakness: causes dyspnea

Exacerbating factors

- **Exertion** (the most common exacerbating factor)
- Pregnancy: has a variable effect on the course of myasthenia:
 - ⇒ Women with myasthenia that is stable prior to pregnancy are likely to remain stable throughout pregnancy, although a small proportion may have post-partum worsening.
 - ⇒ In poorly controlled myasthenia before pregnancy, flares are most likely to occur in the first trimester and the postpartum period.
- Infection

• Drugs:

- - penicillamine toxicity → nephrotic syndrome and myasthenic syndrome.
- ⇒ Quinidine, procainamide
- ⇒ Beta-blockers, calcium channel blockers, verapamil, propafenone,.
- ⇒ Lithium, Tricyclic antidepressants
- ⇒ Phenytoin
- Antibiotics: **gentamicin**, macrolides, guinolones, tetracyclines
 - Aminoglycoside-induced neuromuscular blockade
 - Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis.
 - large doses given during surgery have been responsible for a transient myaesthenic syndrome in patients with normal neuromuscular function.

Investigations

- Autoantibodies (most specific test)
 - ⇒ Antibodies to acetylcholine receptors are seen in 80-90% of cases.
 - ⇒ 100% of patients with thymoma have antibodies
 - ⇒ Antibodies are less commonly seen in disease limited to the ocular muscles
 - ⇒ Seronegative MG (10–20%): negative for AChR antibodies, may be positive for muscle-specific tyrosine kinase antibodies (MuSK antibodies)
 - patients with (MuSK) antibodies are much less likely to have thymic hyperplasia or a thymoma, less responsive to anticholinesterase drugs, and may require more aggressive early immunotherapy than patients who have AChR antibodies.
- Single fibre electromyography (EMG) (most sensitive test)
 - ⇒ **High sensitivity** (92-100%)
 - ⇒ It simultaneously records the variability in potentials of two muscle fibres innervated by an individual axon: jitter.
 - ⇒ shows decremental response following repetitive nerve stimulation
 - ⇒ Electrical recordings of single motor unit activity commonly reveal variation in the latency of the various muscle fibre responses (abnormal jitter)
 - ⇒ Jitter is the most sensitive EMG index in MG but is not specific of the condition.
- CT thorax to exclude thymoma
- CK normal
- Edrophonium test (Tensilon test)
 - ⇒ Used to diagnose MG before AChR antibody test became the common method
 - Symptoms improve rapidly after administration of a short-acting acetylcholinesterase inhibitor

Management

- In mild cases: long-acting anticholinesterase e.g. pyridostigmine
 - \Rightarrow Pyridostigmine \rightarrow cholinesterase inhibitors \rightarrow \uparrow ACh at neuromuscular junctions.
- In more severe disease (with limb weakness or bulbar dysfunction) → immunosuppression
 - ⇒ Prednisolone initially

- Addition of steroid-sparing agents such as mycophenolate mofetil, ciclosporin or azathioprine if necessary.
- In patients with **congenital myasthenia**, anticholinesterase drugs and immunomodulating treatments are not beneficial and **should be avoided**.
- Thymectomy
 - ⇒ Can be beneficial even if a thymoma is not present
 - ⇒ Thymectomy is the following cases:
 - 1. Patients with MuSK antibody-associated MG without a thymoma
 - 2. Late onset disease or
 - 3. Purely ocular disease

Myasthenic crisis

- Definition: acute, life-threatening exacerbation of myasthenic symptoms that leads to respiratory failure
- Epidemiology: affects 15–20% of patients with MG
- Aetiology
 - ⇒ Infection
 - ⇒ Surgery, anesthesia
 - ⇒ Pregnancy
- Differential diagnosis: cholinergic crisis
 - ⇒ Overuse of pyridostigmine → cholinergic crisis (like organophosphate poisoning)
 → bradycardia, hypotension, bronchospasm, abdominal cramping, diarrhea, and flaccid paralysis of the extremities.
 - ⇒ Edrophonium test is your clue (a short-acting acetylcholinesterase inhibitor).
 - In myasthenia gravis, this will lead to a temporary relief of symptoms.
 - In a cholinergic crisis, this will have no effect (or worsen the situation).
 - Managed with Atropine to antagonize cholinergic activity.
- Treatment
 - ⇒ Intravenous immunoglobulins (IVIg 400mg/kg for 5 days)
 - ⇒ Plasmapheresis: usually works quicker but involves more expensive equipment
 - ⇒ Early endotracheal intubation: Elective intubation should be considered if the vital capacity show values are less than 20 mL/kg.

Myasthenic crisis: The patient has marked respiratory weakness with reduced breath count, reduced oxygen saturation, chest expansion and forced vital capacity.

Myasthenic crisis VS Cholinergic crisis

	Myasthenic crisis	Cholinergic crisis
Pupil	Normal	Miosis (constricted pupil)
Fasciculations	None	Present
Heart rate	Tachycardia	Bradycardia
Skin	Cold and faint	Warm and flushed
Bronchial secretion	Normal	Increased

Lambert-Eaton myasthenic syndrome (LEMS)

Definition

 Rare autoimmune disease that reduces neuromuscular transmission, leading to muscle weakness

Prevalence

• Occurs in males more often than females (5:1).

Aetiology

- Paraneoplastic: associated with small-cell lung carcinoma (in ¾ of LEMS cases)
- May also occur independently as an autoimmune disorder.

Pathophysiology

Autoantibodies directed against presynaptic voltage-gated calcium channels (anti-VGCC antibodies) → ↓ Ca2+ influx → ↓ presynaptic vesicle fusion → impaired acetylcholine release in the neuromuscular junction (NMJ)

Features

- Proximal muscle weakness
- Repeated muscle contractions lead to increased muscle strength (in contrast to myasthenia gravis)
- Reduced or absent reflexes (in contrast to myasthenia gravis where the reflexes are normal or brisk)
- Autonomic symptoms: dry mouth, impotence, difficultly micturating.
- Ophthalmoplegia and ptosis are not common (unlike in myasthenia gravis)

Diagnostics

- Active muscle contraction or repeated muscle tapping increases reflex activity.
- Lambert sign: a patient's muscle strength improves with repetitive or ongoing use
- EMG: Repetitive nerve stimulation results in incremental responses.
- Confirmatory test: serologic detection of anti-VGCC antibodies

Treatment

• First-line to improve neuromuscular transmission: amifampridine

Myasthenia gravis VS Lambert-Eaton

	Myasthenia gravis	Lambert-Eaton
Muscle weakness	Proximal muscle weakness: face, neck, limb girdle	Affects lower limbs first
Muscle power following exercise	Becomes weaker	Temporary increase
Reflexes	Normal or brisk	Absence or hyporeflexia
Autonomic dysfunction	None	Common
Antibodies	Antibodies to acetylcholine receptors	Antibody directed against pre-synaptic voltage gated calcium channel
Commonly associated tumor	Thymomas or thymic hyperplasia	Small cell lung cancer

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MRCPUK-part-1-May 2019 exam: A patient of small cell lung carcinoma presents with muscle weakness, spreading from legs to arms + hyporeflexia . C/O dry mouth & erectile dysfunction. Antibodies to which one are most likely to be responsible for these findings? Voltage gated calcium channels

Neurofibromatosis (NF)

NF1: chromosome 17 - as neurofibromatosis has 17 characters

NF2: chromosome 22 - all the 2's

Lisch nodules are seen in neurofibromatosis

Aetiology

- Inherited (50%) Autosomal dominant
- Sporadic mutations (50%): no family history

Pathophysiology

- Mutation of tumor suppressor gene → loss of function → uninhibited cell growth → neurofibroma development
 - ⇒ **NF type 1:** NF1 gene mutation (100% penetrance)
 - Encodes **neurofibromin** protein
 - Located on chromosome 17
 - Inhibition of cell growth and proliferation via inhibition of the Ras signal transduction pathway (Ras activity is inhibited by the stimulation of GTPase)
 - ⇒ **NF type 2:** NF2 gene mutation
 - Encodes merlin protein
 - Located on chromosome 22

Features

NF1	NF2
More common (affects1 in 4,000)	⇒ Less common (Affects around 1 in 100,000)
 Cafê-au-lait spots (≥ 6 spots, 15 mm in diameter) Axillary/groin freckles Peripheral neurofibromas Iris harmatomas (Lisch nodules) in > 90% Seizures and/or focal neurologic signs due to brain lesions (especially meningiomas) Scoliosis Pheochromocytomas 	 ➡ Bilateral vestibular schwannomas (acoustic neuromas) → affecting the vestibulocochlear nerve → tinnitus, hearing loss, or vertigo ➡ Early-onset cataracts, usually bilateral ➡ Multiple cerebral and spinal tumors (especially meningiomas and ependymomas)





Multiple light brown macules with irregular borders (café-aulait spots) is highly suggestive of neurofibromatosis type 1.



Lisch nodules

Pigmented hamartomas on the iris, which are pathognomonic of neurofibromatosis type 1.

Complications

· increased lifetime cancer risk

Diagnostics

- · MRI of the brain and spine with contrast
- Ophthalmological exam
- · Auditory testing
- · Genetic testing

Treatment

- Excision or resection of tumors (e.g., meningiomas)
- Surgery for kyphoscoliosis in NF type 1
- Drugs targeting the mTOR pathway (e.g., sirolimus) to reduce tumor growth

Tuberous sclerosis (TS)

Overview

- Autosomal dominant condition, variable expression
- TS affects about 1 in 10,000 people in the general population
- It is the second most frequent neurocutaneous syndrome after neurofibromatosis.
- Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

Pathophysiology

- $\bullet \;\;$ Mutation of tumor suppressor genes \to loss of function \to unchecked cell growth \to tumor development
- Tumor suppressor genes
 - ⇒ TSC1 gene on chromosome 9 encodes hamartin protein
 - ⇒ TSC2 gene on chromosome 16 encodes tuberin protein

Tuberous sclerosis: presentation

 Cigarettes and coffee with a rough stupid person with a butterfly on his nose while he is dancing

Features

Cutaneous

- Adenoma sebaceum (facial angiofibroma): benign tumor composed of blood vessels and fibrous connective tissue, located around the nose and cheeks (butterfly distribution)
- ⇒ Ash-leaf spots: hypopigmented (white) macules on the trunk and extremities
- ⇒ **Shagreen patch:** flesh-colored papule in the lumbosacral region with an orangepeel appearance
- ⇒ fibromata beneath nails (subungual fibromata)

Neurological

- ⇒ Developmental delay
- ⇒ Epilepsy (infantile spasms is most common form)
- ⇒ Autism
- ⇒ intellectual impairment
- ⇒ Fibromas may also develop within the central nervous system, where they calcify typically in the periventricular area.

Cardiac rhabdomyoma

- ⇒ Present in > 50% of affected individuals
- ⇒ May cause symptoms of mitral regurgitation and/or congestive heart failure
- Renal disease: Renal cysts, Angiomyolipoma, Renal carcinoma

Diagnostics

- ECG: cardiac rhabdomyoma can cause ventricular hypertrophy and arrhythmias
- · EEG: seizure activity
- Echocardiography: rhabdomyoma (common in the apex of the left ventricle)
- · Abdominal MRI: renal cyst, angiomyolipoma, and/or carcinoma
- Contrast cerebral CT/MRI
 - ⇒ Tumors (e.g., giant cell astrocytomas)
 - ⇒ Enlarged ventricles (tumors in the periventricular area commonly cause obstructive hydrocephalus)
- Genetic testing

Treatment

- Seizure control
- mTOR inhibitors: to treat renal angiomyolipoma and inoperable giant cell astrocytoma
- Removal of angiofibroma (laser treatment or electrosurgery)
- · Surgery in the case of:
 - ⇒ Obstructive hydrocephalus (with ↑ ICP)
 - ⇒ Drug-resistant seizures

MRCPUK-part-1-January 2018 exam: Generalised seizure + patches of hypopigmented skin + fibromata under finger nails. What is the most likely diagnosis? Tuberous sclerosis

MRCPUK-part-1-May 2017 exam: H/O hypovolaemic shock. CT abdomen reveals a haemorrhagic lesion in the right kidney. biopsy shown it to be an angiomyolipomata. What is the most likely underlying diagnosis? Tuberous sclerosis

Paraneoplastic syndromes affecting nervous system

Lambert-Eaton myasthenic syndrome

- associated with small cell lung cancer (also breast and ovarian)
- antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system
- can also occur independently as autoimmune disorder

Anti-Hu

- associated with small cell lung carcinoma and neuroblastomas
- sensory neuropathy may be painful
- · cerebellar syndrome
- encephalomyelitis

Anti-Yo

- associated with ovarian and breast cancer
- cerebellar syndrome

Anti-GAD antibody

- · associated with breast, colorectal and small cell lung carcinoma
- · stiff person's syndrome or diffuse hypertonia

Anti-Ri

- · associated with breast and small cell lung carcinoma
- ocular opsoclonus-myoclonus

Anti-Purkinje cell antibodies

- subacute cerebellar degeneration
- peripheral neuropathy due to a remote (autoimmune) effect of gynecologic or breast carcinoma.

GM1 antibodies (Glycolipid ganglioside-monosialic acid) associated with

- Lower motor neuron syndromes
- Amyotrophic lateral sclerosis
- · Multiple sclerosis
- · Other multifocal neuropathies and
- Systemic lupus erythematosus (SLE) with central nervous system involvement.

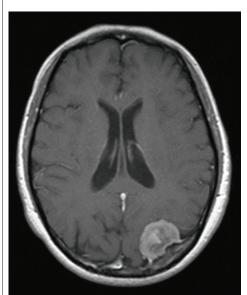
MRCPUK-part-1-May- 2019 exam: Ovarian cancer + unsteadiness, nystagmus and past-pointing. Which antibody is most likely to be present?

→ Anti-Yo

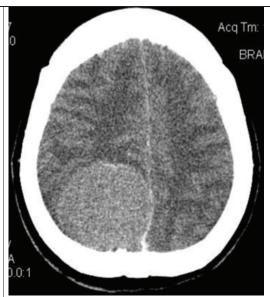
Brain tumours

The majority of adult tumours are supratentorial, whereas the majority of childhood tumours are infratentorial.

Type of tumour	Features
Glioblastoma multiforme	The most common primary brain tumour in adults, accounts for about 20% of all cerebral tumours. Histology: Pleomorphic tumour cells border necrotic areas Pseudopalisading tumor cells on brain biopsy are a characteristic
Meningioma	The second most common primary brain tumour in adults Histology: Spindle cells in concentric whorls and calcified psammoma bodies
Schwannoma	 Often seen in the cerebellopontine angle: acoustic neuroma Bilateral schwannoms are seen in neurofibromatosis Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)
Pilocytic astrocytoma	The most common primary brain tumour in children Histology: Rosenthal fibres (corkscrew eosinophilic bundle)
Medulloblastoma	More common in children Found exclusively in the posterior fossa Metastases through the CSF Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures
Ependymoma	Commonly seen in the 4th ventricle May cause hydrocephalus Histology: perivascular pseudo rosettes
Oligodendroma	Benign, slow-growing tumour common in the frontal lobes Histology: Calcifications with 'fried-egg' appearance
Haemangioblastoma	Vascular tumour of the cerebellum Associated with von Hippel-Lindau syndrome Histology: foam cells and high vascularity
Pituitary adenoma	Most common type is a prolactinoma May present with bitemporal hemianopia
Craniopharyngioma	Most common paediatric supratentorial tumour The commonest presentation in young patients is growth failure and delayed puberty. CT: suprasellar calcified cyst Histology: Derived from remnants of Rathke pouch
Metastases	 Most common type of brain tumour The <u>most common sites</u> that metastasise to the brain is <u>lung (44%)</u>, therefore, a <u>chest x ray would be the initial investigation of choice</u>. Initial treatment: <u>Start dexamethasone immediately</u>



Meningioma - MRI showing the typical well-circumscribed appearance. A dural tail can be where the tumour 'connects' to the dura. It is seen in around 65% of meningiomas.



The CT shows a well defined spherical mass in the right posterior falx cerebri consistent with a **meningioma**. There is mild oedema and mass effect on the right lateral ventricle. The tumour is straddling the inferior surface of the falx.



Glioblastoma multiforme - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the more homogenous meningioma above.

Von Hippel-Lindau syndrome (VHL)

Early age SAH occur in Von Hippel Lindau

Overview

- Autosomal dominant condition
- VHL gene is tumor suppressor gene on the short arm of chromosome 3
- Deletion of VHL gene \rightarrow loss of function \rightarrow tumor and cyst development

Features

- Vascular tumors (hemangioblastoma): Common in retina, cerebellum, brainstem, and/or spine

 - ⇒ Retinal haemangiomas: vitreous haemorrhage → vision loss
 - ⇒ Hemangioblastomas are highly vascularized lesions whose cells have hyperchromatic nuclei.
- Renal cysts (premalignant), renal cell carcinoma
- Phaeochromocytoma
- Extra-renal cysts: epididymal, pancreatic, hepatic
- Endolymphatic sac tumours → hearing loss, tinnitus, and/or vertigo (bilateral disease is a pathognomonic feature)

Cerebrospinal fluid (CSF)

Overview

- CSF Produced by ependymal cells of choroid plexuses in the lateral, third, and fourth ventricles by filtration of plasma.
- Approximately 500ml of cerebrospinal fluid is produced each day.
- It is absorbed into the circulation via the arachnoid villi.
- CSF is largely similar to plasma in composition, but has much lower levels of protein.

What type of cells produce cerebrospinal fluid?

Ependymal cells

Normal values of cerebrospinal fluid (CSF)

- Pressure = 60-150 mm (patient recumbent)
- Protein = 0.2-0.4 g/l
- Glucose = > 2/3 blood glucose (60% of serum levels)
- Cells: red cells = 0, white cells < 5/mm³

Conditions associated with raised lymphocytes

- Viral meningitis/encephalitis
- TB meningitis
- Partially treated bacterial meningitis
- Lyme disease
- · Behcet's, SLE
- Lymphoma, leukaemia

Conditions associated with raised protein levels

- Guillain-Barre syndrome
- Tuberculous, fungal and bacterial meningitis
- · Viral encephalitis

Disruption of the blood-brain barrier (i.e., infections, autoimmune diseases, CNS malignancies) or intrathecal production of IgG (i.e, multiple sclerosis, CNS infections such as Lyme disease) \rightarrow increased immunoglobulins (oligoclonal bands) \rightarrow increased CSF protein

Vertebral level and corresponding structure

- C4 → Hyoid bone, **Bifurcation of common carotid**
- C5 → Thyroid cartilage, Carotid pulse palpated
- C6 → Cricoid cartilage, Beginning of trachea, Beginning of esophagus
- T2 → Sternal notch, Arch of aorta
- T12 → aortic opening
- T4 → Sternal angle, Junction of superior and inferior mediastinum, Bifurcation of trachea
- T8 → Inferior vena caval hiatus (opening in the diaphragm)
- T9 → Xiphisternal joint
- T10 → Esophageal hiatus (opening in the diaphragm)
- T11 → Upper pole of left kidney
- T12 → Upper pole of right kidney, **Aortic hiatus** (opening in the diaphragm)
- L3 → Umbilicus
- L4 → Iliac crest, Bifurcation of aorta
- L1 → End of spinal cord
- S1 → Beginning of sigmoid colon
- S2 → End of dural sac (and CSF)
- S3 → End of sigmoid colon

The spinal cord terminates at lower border of L1 vertebra

Post-lumbar puncture headache

Epidemiology

- Headache following lumbar puncture (LP) occurs in approximately **one-third** of patients.
- More common in young females with a low body mass index

Pathophysiology

- Leaking of cerebrospinal fluid from the dura is the most likely explanation.
 Typical features
- Usually develops within 24-48 hours following LP but may occur up to one week later
- May last several days
- Worsens with upright position
- Improves with recumbent position

Factors which may contribute to headache	Factors which do not contribute to headache	
 Increased needle size Direction of bevel Not replacing the stylet Increased number of LP attempts Use of a Quincke (sharp) needle 	 Increased volume of CSF removed Bed rest following procedure Increased fluid intake post procedure Opening pressure of CSF Position of patient 	

What is the most appropriate type of needle to use in lumbar puncture?

- **○** 20G Sprotte[®] (atraumatic) needle
- Studies show that smaller atraumatic needles reduce the risk of post-lumbar puncture headache.

Management

- Supportive initially (analgesia, rest)
- If pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma
- Treatment options include: blood patch, epidural saline and intravenous caffeine

Spinal cord lesions

Disorder	Tracts affected	Clinical notes
Brown-Sequard syndrome (spinal cord hemisection)	Lateral corticospinal tract Dorsal columns Lateral spinothalamic tract	Ipsilateral spastic paresis below lesion Ipsilateral loss of proprioception and vibration sensation Contralateral loss of pain and temperature sensation
Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency)	Lateral corticospinal tracts Dorsal columns Spinocerebellar tracts	Bilateral spastic paresis Bilateral loss of proprioception and vibration sensation Bilateral limb ataxia
Friedrich's ataxia	Same as subacute combined degeneration of the spinal cord (see above)	Same as subacute combined degeneration of the spinal cord (see above)
Anterior spinal artery occlusion	Lateral corticospinal tracts Lateral spinothalamic tracts	Bilateral spastic paresis Bilateral loss of pain and temperature sensation
Syringomyelia	Ventral horns Lateral spinothalamic tract	Flaccid paresis (typically affecting the intrinsic hand muscles) Loss of pain and temperature sensation
Multiple sclerosis	Asymmetrical, varying spinal tracts involved	Combination of motor, sensory and ataxia symptoms
Neurosyphilis (tabes dorsalis)	Dorsal columns	Loss of proprioception and vibration sensation

Metastatic spinal cord compression

Metastatic spinal cord compression:

- Dexamethasone should be given immediately (to reduce inflammation around the cord)
- Then Urgent radiotherapy is the definitive treatment.

Epidemiology

 Spinal cord compression is an oncological emergency and affects up to 5% of cancer patients.

Causes

 Extradural compression accounts for the majority of cases, usually due to vertebral body metastases. • It is more common in patients with lung, breast and prostate cancer

Features

- back pain
 - ⇒ the earliest and most common symptom
 - ⇒ may be worse on lying down and coughing
- · lower limb weakness
- sensory changes: sensory loss and numbness
- neurological signs depend on the level of the lesion.
 - ⇒ **Lesions above L1** usually result in upper motor neuron signs in the legs and a sensory level.
 - ⇒ Lesions below L1 usually cause lower motor neuron signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion

Diagnosis

 The definitive investigation in this case is an MRI of the vertebral column to look for vertebral collapse or other vertebral disease.

Management

- high-dose oral dexamethasone
 - Corticosteroids should be started immediately, even before the diagnosis is confirmed radiologically,
 - ⇒ usually with dexamethasone 16 mg STAT followed by 8mg BD (either oral or IV is acceptable).
 - ⇒ Dexamethasone given for spinal cord compression can be given via any available route. Giving it intravenously offers no significant advantage over giving it orally.
 - ⇒ temporarily reduce oedema related to the underlying tumour and thus have a positive impact on neurological deficit,
 - ⇒ the response to steroids predicts neurological response to subsequent definitive treatment which should be started within 24 hours.
- urgent oncological assessment for consideration of radiotherapy or surgery
 - ⇒ **Urgent radiotherapy is the definitive treatment**, although neurosurgical opinion should be sought in order to ensure that surgical decompression is not required.
 - ⇒ Treatment is effective in 90% of patients if the diagnosis is made early.
 - ⇒ As L1 is being affected, this can be arranged urgently, rather than immediately. Immediate radiotherapy is necessary for lesions above L1.
- Spinal stabilisation surgery
 - ⇒ should be urgently considered for:
 - Patients with spinal metastases and imaging evidence of structural spinal failure with spinal instability.
 - Patients with spinal metastases and mechanical pain resistant to conventional analgesia, even if they have been completely paralysed.
 - ⇒ Preoperative radiotherapy should not be performed, although postoperative radiotherapy can be offered to patients with a satisfactory outcome, once the wound has healed.

Prognosis

- Pre-treatment ambulatory function is the best determinant of post treatment gait function
 - ⇒ 80% of patients will maintain mobility if ambulatory function is good at presentation.

Disc prolapse

Loss of sensation in the upper outer thigh is consistent with nerve root compression caused by a prolapsed vertebral disc.

Pathophysiology

- The intervertebral disk consists of a dense outer ring (annulus fibrosus) and a gelatinous core (nucleus pulposus).
- disk protrusion or herniation through the annulus fibrosus into the central canal → adjacent nerve root impingement → sensorimotoric deficits in affected nerve root
- The herniation of the nucleus pulposus is most commonly in the **posterolateral direction** as it is the weakest part of the surrounding annulus fibrosus.
- The affected nerve root is typically the one below the level of disc herniation

Intervertebral discs usually protrude/herniate posterolaterally, as the posterior longitudinal ligament is thinner than the anterior longitudinal ligament.

Common sites of prolapse

- . Most often occurs in the lumbar spine
 - ⇒ (95% of disc herniations occur at the L4-L5 and L5-S1 level).
 - ⇒ L5–S1 (most common site)
 - ⇒ L4–L5 (second most common site)
- Cervical and thoracic disc herniations are rare

Causes

- Disc degeneration (the most common cause)
- Trauma

Features

- Acute onset of severe neck or back pain
 - ⇒ Radicular pain: pain that radiates to the legs (sciatic pain) or arms
 - ⇒ The pain is either stabbing in nature or resembles an electric shock
- Features of radiculopathy: lower motor neuron signs of the affected nerve root (typically unilateral)
 - ⇒ Paresthesia of the affected dermatome
 - ⇒ Muscle weakness
 - ⇒ Absent or diminished deep tendon reflexes
- Character of pain
 - ⇒ Pain increases with pressure (e.g., from coughing or sneezing)
 - ⇒ Pain is typically <u>better with</u> rest: if it is **unremitting or worse on resting** you should **consider other causes** such as bony **metastases** or infection.
 - ⇒ Changing position reduces the pain

Management

- Gentle mobilisation and physiotherapy (the management of choice): most patients will make a spontaneous improvement within 4–6 weeks.
- Surgery (Microdiscectomy or open discectomy)
 - ⇒ is a potential treatment options for patients with radiologically proven nerve root compression and severe symptoms or symptoms that do not resolve with conservative measures.
- Local corticosteroid injection: symptomatic relief if not fit for surgery

compression Level of **Features** compression Sensory loss from anterior thigh to medial aspect of lower leg L3 nerve root compression Weak quadriceps ⇒ ↓ knee reflex Positive femoral stretch test Caused by L3/4 disc prolapse L4 nerve root Sensory loss over the thigh and anterior aspect of knee compression Weak quadriceps ⇒ ⊥ knee reflex Positive femoral stretch test Caused by L4/5 disc prolapse Sensory loss dorsum of foot and lateral aspect of leg L5 nerve root Weakness in foot and big toe dorsiflexion ('foot drop') compression Reflexes intact Positive sciatic nerve stretch test. Caused by L5/S1 disc prolapse Sensory loss posterolateral aspect of leg (posterior calf and the S1 nerve root plantar surface of the foot) and lateral aspect of foot compression Weakness in plantar flexion of foot ⇒ ↓ ankle reflex Positive sciatic nerve stretch test

Prolapsed cervical disc (Cervical radiculopathy)

Overview

- Most commonly affects the C5/C6 and C6/C7 vertebrae.
- Central protrusions can lead to symptoms of spinal cord compression.
- Posterolateral protrusions can cause a stiff neck, pain radiating to the arm, weakness of the muscles affected by the nerve root and depressed reflexes.
- X-ray may shows narrowing of the disc space between the C5 and C6 vertebrae.

Deferential diagnosis

- · Cervical spondylosis
 - ⇒ occurs as a result of osteoarthritis.
 - ⇒ Muscle weakness is uncommon
 - ⇒ X-ray changes:
 - Disc spaces can be narrowed
 - Osteophytes seen in the central and posterior intervertebral joints.
- Cervical rib
 - ⇒ can present with similar symptoms but the X-ray would be diagnostic (showing the presence of a cervical rib).

Spasmodic torticollis

- ⇒ sudden onset of a stiff painful neck with torticollis can occur in adults due to spasm of the trapezius and sternocleidomastoid muscles.
- ⇒ X-ray of the cervical spine is usually normal.

Common cervical radiculopathies

	Sensory deficits	Motor deficits	Reduction of reflexes
C5 radiculopathy	Anterior shoulder	Biceps and deltoid	Biceps
C6 radiculopathy	From upper lateral elbow over radial forearm up to thumb and radial side of index finger	Biceps and wrist extensors	Biceps Brachioradialis
C7 radiculopathy	 Palmar: fingers II–IV (II ulnar half, III entirely, IV radial half) Dorsal: medial forearm up to fingers II–IV (II ulnar half, III entirely, IV radial half) 	Triceps and wrist flexors, finger extensors	Triceps
C8 radiculopathy	Dorsal forearm up to dorsal and palmar area of fingers IV (ulnar half)	Finger flexors	None

Conus medularis syndrome

Conus medullaris syndrome is caused by compression of the T12-L2 cord and nerve roots, and therefore results in a mix of upper and lower motor neuron signs.

- Mixed upper and lower motor neurone signs.
 - ⇒ These include bilateral distal weakness with increased tone and hyper-reflexia, fasciculation, positive Babinski sign and clonus.
 - Cauda equina would give just LMN signs,
- · Sensory loss is most marked in the perianal region.
 - □ In Amyotrophic lateral sclerosis (the commonest form of motor neurone disease),
 There would be a mixture of UMN and LMN signs; however, they do not have any
 sensory signs or incontinence.
- It is much rarer than cauda equina syndrome.

Canua	medullaris	avndrama	VC	Coulda	aduina	avndrama
Collus	illeuullalis :	SVIIUIUIIIE	v٥	Cauua	euuma	SVIIUIUIIIE

	Conus medullaris syndrome	Cauda equina syndrome
Presentation	Sudden and bilateral	Gradual and may be unilateral leg sings initially
Reflexes	Knee jerk preserved Ankle jerk affected	Both knee and ankle jerk affected
Radicular pain	Less severe	More severe
Sensory	Numbness often localised peri-anal area (often bilateral)	Numbness often localised saddle area (often unilateral)
Motor	Symmetrical Upper motor signs (hyperreflexic distal paresis, less than cauda equina, may be fasciculation)	May be asymmetrical Lower motor signs (areflexic paraplegia, atrophy, fasciculations is rare)
Impotence	Frequent	Often less marked
Sphincter disfunction	Urinary retention and atonic anal sphincter present early in disease (can cause overflow urinary incontinence)	Urinary retention usually present later in course of disease
Low back pain	More marked	Less marked

Conus medullaris syndrome and cauda equina syndrome are medical emergencies requiring immediate surgical intervention.

Cauda equina syndrome

Cauda equina syndrome is caused by compression of the lumbosacral roots, from L1 down to S5, and therefore results in only lower motor neuron signs.

Causes

- herniation of a lumbar disc (at L4/L5 and L5/S1)
- tumour (metastases, lymphoma, primary spinal tumours)
- trauma
- infection (epidural abscess).
- Others: ankylosing spondylitis, Paget's disease, and congenital spinal stenosis.

Features

- lower motor neuron signs: flaccid paraplegia, areflexia, flexor plantar reflexes
- unilateral or bilateral lower limb motor and/or sensory abnormality
- low back pain
- Whilst classically patients present with a sensory level, this is variable in clinical practice.
- bladder retention and overflow incontinence (bowel and/or bladder dysfunction with saddle and perineal anaesthesia)
- Saddle anesthesia.
 - ⇒ Patients usually describe numbness and/or "pins-and-needles" sensations of the groin and inner thighs which would contact a saddle when riding a horse. This reflects involvement of the S3-S5 roots.

Diagnosis

• MRI is the investigation of choice

Autonomic dysreflexia

Definition

 A clinical syndrome occurs in patients who have had a spinal cord injury at, or above T6 spinal level (85% of patients).

Mechanism

- A strong sensory input (most commonly urine retention or constipation) → travels up the spinal cord → massive reflex sympathetic surge from the thoracolumbar sympathetic nerves → widespread vasoconstriction, most significantly in the subdiaphragmatic (or splanchnic) vasculature → hypertension crisis
- The brain detects this hypertensive crisis through intact baroreceptors in the neck delivered to the brain through cranial nerves IX and X.
- The brain attempts two maneuvers to decrease BP:
 - 1. by sending descending inhibitory impulses of sympathetic surge which are unable to travel because of the spinal cord injury at T6 or above.
 - 2. by slowing the heart rate through an intact vagus (parasympathetic) nerve; however, this compensatory bradycardia is inadequate, and hypertension continues.
- In summary, the sympathetics prevail below the level of neurologic injury, and the parasympathetic nerves prevail above the level of injury.

Triggers

- urinary retention (cystitis, retention of urine or a blocked catheter): most common
- constipation (faecal impaction)

Features

- unbalanced physiological response, characterised by :
 - ⇒ extreme hypertension, may leads to complications
 - ⇒ flushing and sweating above the level of the cord lesion
 - ⇒ Agitation
 - ⇒ Bradycardia

Treatment

- recognition and removal of the triggers.
- Vasodilators such as calcium antagonists may be used to treat the hypertension.

Spastic paraparesis

Definition

 Spastic paraparesis describes an upper motor neuron pattern of weakness in the lower limbs

Causes

- demyelination e.g. multiple sclerosis
- · cord compression: trauma, tumour
- parasagittal meningioma (Spinal meningioma)
 - ⇒ progressive symptoms (not acute), well-defined sensory level
 - ⇒ MRI of the spine with gadolinium contrast is the investigation of choice
- tropical spastic paraparesis
 - ⇒ classic presentation → HTLV-1 positive patient presenting with paraparesis and urinary retention due to Adult T-cell lymphoma (ATL) caused by human Tlymphotropic virus type 1 (HTLV-I)

- transverse myelitis e.g. HIV
- syringomyelia
- · hereditary spastic paraplegia
- · osteoarthritis of the cervical spine

Sudden onset	Progressive onset	
Anterior spinal artery infarct	demyelination e.g. multiple sclerosis	
 Osteoporotic thoracic spine 	Metastatic carcinoma	
collapse	Spinal meningioma	
Prolapsed thoracic disc		

Absent ankle jerks, extensor plantars

Overview

- Typically caused by lesion producing both upper motor neuron (extensor plantars) and lower motor neuron (absent ankle jerk) signs
- Mixture of UMN and LMN signs

Causes

- · subacute combined degeneration of the cord
- · motor neuron disease
- Friedreich's ataxia (usually presents by age 30)
- Syringomyelia
- taboparesis (syphilis)
- HIV
- Spinal AVM
- · conus medullaris lesion

Which neurological finding is most helpful in differentiating subacute combined degeneration of the cord from multiple sclerosis?

→ Absent ankle jerk

Subacute combined degeneration of spinal cord (SACDC)

Basics

- due to vitamin B12 deficiency
- vitamin B12 deficiency → increased levels of methylmalonic acid → impairs spinal cord myelinization.
- · dorsal + lateral columns affected
- if untreated stiffness and weakness persist

Features

- joint position and vibration sense lost first then distal paraesthesia
- upper motor neuron signs typically develop in the legs, classically:
 - ⇒ extensor plantars,
 - Plantars are initially flexor, and later extensor.
 - ⇒ brisk knee reflexes.
 - (but may be increased, normal or absent)
 - ⇒ absent ankle jerks

- On presentation, 50% of patients have absent ankle reflexes with hyperreflexia at the knees.
- · Spastic paresis
- Gait abnormalities (spinal ataxia, positive Romberg's test)
- Lhermitte's phenomenon is typically present in multiple sclerosis, but may also occur in subacute combined degeneration of the cord.

Diagnosis

MRI typically shows increased signal on T2~weighted imaging in the dorsal columns

Transverse myelitis

Overview

- inflammation across the entire width of one level, or segment of the spinal cord.
- Characterised by acute or subacute motor, sensory and autonomic spinal cord dysfunction.
- the thoracic region of the spinal cord is most commonly affected.

Causes

- Acute infection
 - ⇒ Viral: most commonly
 - ⇒ Bacterial infections: syphilis, Lyme disease
- Post-infections or vaccination (immune mediated)
- Autoimmune (SLE, MS)

Features

- Course of the disease: develop over hours to days, and are usually bilateral
- Motor dysfunction (e.g., paresis, paraplegia)
- · Sensory dysfunction
 - ⇒ Sensory level is characteristic.
 - ⇒ Midline or dermatomal neuropathic pain can be present.
- Autonomic dysfunction
 - ⇒ Sphincter dysfunction
 - Urinary incontinence or retention
 - Bowel incontinence or constipation
 - ⇒ Sexual dysfunction is common but vary in severity.

Investigation

- MRI
 - ⇒ to rule out the presence of structural lesions,
 - ⇒ to determine the presence of myelitis, which enhances with gadolinium in the acute phase.
 - Evidence of inflammation can be confirmed via <u>gadolinium-enhanced MRI</u>.
 - ⇒ There may be more than one area of myelitis, and the lesions usually span at least two vertebral segments.
 - ⇒ there is variable enlargement of the spinal cord
 - ⇒ In the acute phase the MRI may be normal.
- CSF analysis: pleocytosis and/or elevated IgG index

Treatment

- First-line: immediate high-dose IV corticosteroids
- Plasma exchange can be given to those who fail to respond.
- Patients with demyelinating disease can be started on long term immunosuppression.

Prognosis

- · Predictors of poor prognosis
 - ⇒ rapidly progressive course
 - ⇒ severe weakness
 - ⇒ hypotonia
 - ⇒ areflexia
- Improvement chances
 - ⇒ time frame: improvement can take three months and longer to develop
 - ⇒ percentage: 50 70% of patients have partial or complete recovery.
 - One-third of patients recover with little or no sequelae
 - One-third are left with a moderate degree of permanent disability
 - One-third are left with severe disabilities
- Risk of future MS: Depends on the pattern of transverse myelitis:
 - ⇒ complete transverse myelitis: only 5-10% will be diagnosed with MS
 - ⇒ incomplete transverse myelitis: 60-90% will be diagnosed with MS within 5 years.

Syringomyelia

Syringomyelia - spinothalamic sensory loss (pain and temperature)

Syringomyelia typically causes loss of reflexes, spinothalamic sensory loss (pain and temperature), and weakness. It can be asymmetrical initially

Definition

 Syringomyelia is a <u>degenerative</u> disease of the spinal cord that is characterized by a fluidfilled cavity within the cervical spinal cord.

Pathophysiology

- · development of cavity (syrinx) within the spinal cord
- Syrinx (fluid-filled cavitation) in the central spinal cord, usually cervical. This can elongate
 and enlarge, causing → compression of the corticospinal and spinothalamic tracts and
 anterior horn cells.
- · if extends into medulla then termed syringobulbia
- Most of the cavities in syringomyelia lie between the second cervical and the ninth thoracic vertebrae.
 - ⇒ most commonly affecting the cervical region
- collection of fluids within the central canal of the spinal cord →enlargement spinal canal, leading to damage of the crossed fibers (anterior white commissure) of the spinothalamic tract → loss of pain and temperature sensation in the upper extremities

Epidemiology

- more common in men than women
- usually presents in the 20s and 30s although it can present later in life.

Causes

- Arnold-Chiari malformation type I → impaired cerebrospinal fluid circulation
 - ⇒ The most common cause
- · arachnoiditis,
- meningeal carcinomatosis,
- space-occupying lesions
- Post-traumatic syringomyelia

- ⇒ complicate up to 4% of spinal cord injury
- ⇒ often presents with pain, which spreads upwards from the initial injury site.
- · idiopathic.

Features

- maybe asymmetrical initially
- slowly progressive sensory and motor symptoms, possibly over years
- motor: wasting and weakness of arms
- sensory: spinothalamic sensory loss (pain and temperature)
 - ⇒ bilateral loss of pain and temperature sensation in the upper extremities.
 - ⇒ fine touch sensation, vibration and proprioception are preserved
- · loss of reflexes, bilateral upgoing plantars
- · Horner's syndrome,
 - ⇒ seen in advanced syringomyelia due to disruption of sympathetic trunk neurons.
- · Bladder, bowel and sexual dysfunction can develop

Investigations

MRI is the investigation of choice

- MRI of the spinal cord
 - ⇒ the diagnostic modality of choice.
 - ⇒ MRI enhanced with gadolinium has more sensitivity than regular MRI.
- Myelography
 - ⇒ used to confirm the diagnosis but was associated with more deterioration

Localization of the lesion

- At syrinx (there is anterior horn cell involvement) → lower motor neuron pattern of weakness.
- At central decussating fibres (spinothalamic tract) → dissociated sensory loss with late development of neuropathic arthropathy.
- At corticospinal tracts below the level of the syrinx results in spastic paraparesis.

Deferential diagnosis

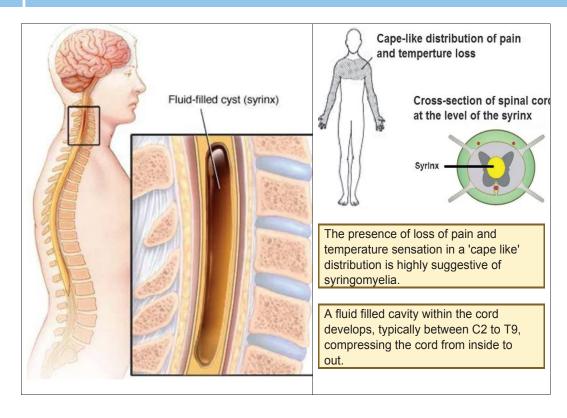
- Amyotrophic lateral sclerosis → NO <u>sensory</u> deficits.
- Anterior spinal artery thrombosis
 - ⇒ characterised by loss of motor function <u>below the level of injury</u>, loss of pain and temperature sensations, and preservation of proprioception, fine touch and vibration.
- Post-traumatic spinal stenosis
 - ⇒ result in neurological changes **below the level** of stenosis.

Management

The mainstay of the treatment of is surgery.

MRCPUK-part-1-May 2010: feature of weakness & wasting of the small muscles of the hand. Which one of the following features would most support a diagnosis of syringomyelia?

→ Loss of temperature sensation in the hands



Arnold-Chiari malformation (CM)

Definition

• Arnold-Chiari malformation describes the downward displacement, or herniation, of the cerebellar tonsils through the foramen magnum.

Causes

· may be congenital or acquired through trauma.

Pathophysiology

- Symptoms of Arnold-Chiari malformation, type I develop as a result of three pathophysiological consequences of the disordered anatomy:
 - 1. compression of the medulla and upper spinal cord,
 - 2. compression of the cerebellum,
 - 3. disruption of cerebrospinal fluid flow through the foramen magnum.

Classification

- classified by extent with which parts of the brain protrude into the spinal canal.
 - ⇒ Chiari I malformation,
 - the only type that can be acquired or can remain asymptomatic until late childhood or early adulthood.
 - characterized by:
 - the time of onset (late childhood/early adulthood) and
 - the downward herniation of cerebellar tonsils, without the involvement of brainstem tissue.

- symptoms due to obstruction of cerebrospinal fluid flow.
- ⇒ more severe types of Chiari malformations would involve additional herniation
 of brainstem tissue (Types II and III) or incomplete development of the cerebellum as
 a whole (Type IV).

Features

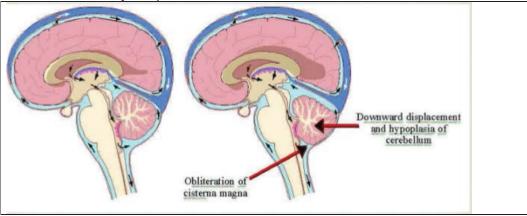
- non-communicating hydrocephalus may develop as a result of obstruction of cerebrospinal fluid (CSF) outflow
- neck pain
- Occipital headache
 - ⇒ exacerbated by cough, valsalva maneuver and exercise.
- syncope due to intermittent obstructive hydrocephalus.
- changes in balance, and poor hand coordination
- Syringomyelia
- Downbeat nystagmus is classically associated with lesions at the foramen magnum (Arnold-Chiari malformation)

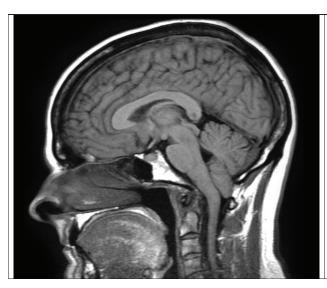
Investigations

MRI brain: → Narrow posterior fossa

Treatment

- type II and III CM and in symptomatic type I CM
 - ⇒ Surgery
- asymptomatic type I CM:
 - ⇒ Surveillance: annual MRI of the brain to look for development of syringomyelia and/or hydrocephalus





MRI showing herniation of the cerebellar tonsils through the foramen magnum consistent with a Chiaria I malformation

Anterior spinal artery thrombosis

Anterior spinal artery thrombosis → Sudden paralysis and loss of pain and temperature sensation and preservation of fine touch, vibration, and proprioception below the level of the lesion.

Vibration and proprioception are typically spared because of an intact dorsal column

Anterior spinal artery infarct occurs at the 'watershed' T4-T6 and would cause symptoms primarily in the lower limb and a sensory level.

- it supplies, roughly the anterior 2/3 of the cord.
- segments of the cord in the watershed area between the branches (around T2–T4) are vulnerable to ischaemia.

Sequelae

- Occlusion of the anterior spinal artery infarcts the ventral portion of the cord.
- affects the structures found at the front of the spine
 - ⇒ corticospinal tracts (motor neurons)
 - ⇒ spinothalamic tracts (pain/temperature sensation).

Feature

- Acute (within hours)
 - ⇒ Back or chest pain
 - ⇒ Spinal shock
 - Bilateral loss of temperature and pain sensation, motor function (flaccid paraparesis or quadriparesis), and autonomic function (bladder, bowel, and sexual dysfunction, orthostatic hypotension) below the level of the lesion
 - reflexes are diminished

- Absent Bulbocavernosus reflex: squeezing the glans penis or pulling on a Foley catheter while digitally palpating the contraction of the anal sphincter
- Late (after days or weeks)
 - ⇒ Continued sensory and autonomic dysfunction
 - Power is reduced below the hips
 - Pain and temperature sensation are lost to the waist.
 - ⇒ **Spastic** paraparesis or quadriparesis (increased muscle tone)
 - ⇒ Hyperreflexia
- Light-touch sensation, vibration and proprioception (joint-position sense) are normal because these are carried in the dorsal columns that are supplied by the posterior spinal artery.
- Injury level
 - Anterior spinal cord lesions above **cervical vertebra 6** will result in **tetraplegia** with involvement of the upper and lower extremities.
 - injuries from **T1-T6** have normal upper extremity, although abdominal and chest muscles may be affected with diminished respiratory excursion.
 - ⇒ The region of **thoracic vertebra 6** is the thoracic watershed zone; lesions below this level result in loss of bowel, bladder, and sexual functions.

Anterior spinal arteries supply corticospinal and spinothalamic tracts, and anterior horns of the grey matter.

What are the diagnostic possibilities of a lesion involve the anterior two thirds of the spinal cord which **spares light touch**, **vibration and position sense**, but causes loss of pain and temperature sensation distally?

The diagnostic possibilities include:

- 1- anterior spinal artery occlusion → sudden onset
- 2- intramedullary spinal cord metastasis

Types of incomplete spinal cord syndromes

• All types present with dissociated sensory loss: a pattern of selective sensory loss ("dissociation of modalities"); suggests a focal lesion of a single tract within the spinal cord

	Affected spinal tracts	Etiology	Clinical features
Central cord syndrome (most common)	Bilateral central corticospinal tracts and lateral spinothalamic tracts	Hyperextension injury (e.g., car crash) associated with chronic cervical spondylosis Spinal cord compression	Bilateral paresis: upper > lower extremities
Anterior cord syndrome	Corticospinal and spinothalamic tracts	 Trauma (e.g., penetrating injury, burst fracture of vertebra) Occlusion of anterior spinal artery 	Bilateral motor paralysis, loss of pain and temperature sensation, and autonomic dysfunction below the level of the lesion
Posterior cord syndrome	Bilateral posterior columns	 Trauma (e.g., penetrating injury) Occlusion of the posterior spinal artery Multiple sclerosis 	Ipsilateral loss of proprioception, vibration, and touch sensation below the level of the lesion
Brown-Séquard syndrome (hemisection syndrome)	Hemisection of the cord	 Trauma (e.g., penetrating injury) Spinal cord compression 	Ipsilateral

Diagnosis

• **Spinal MRI** (best confirmatory test): excludes soft-tissue lesions (e.g., tumors, hematomas), bone lesions, and detects spinal cord parenchyma abnormalities (e.g., infarction)

Brown-Séquard's syndrome

Definition

• Thoracic spinal cord lesion produced by a hemisection of the spinal cord.

Causes

- trauma, (most commonly)
- tumours, and
- · multiple sclerosis.

Features

- Ipsilateral
 - ⇒ Weakness (paralysis)
 - ⇒ <u>loss of position and vibration</u> below the lesion (dorsal column dysfunction)
 - ⇒ Horner syndrome,
 - If the lesion is above the spinal cord level T1, due to damage of the oculosympathetic pathway.
- Contralateral
 - **⇒** loss of pain and temperature.

Diagnosis

MRI is the imaging of choice in spinal cord lesions

Management

· Steroids may decrease cord swelling.

Lower back pain

Overview

- Lower back pain (LBP) is one of the most common presentations seen in practice.
- Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	May be acute or chronic Pain worse in the morning and on standing On examination there may be pain over the facets. The pain is typically worse on extension of the back
Spinal stenosis	Usually gradual onset Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. pain is worse with walking downhill and less with walking uphill. Resolves when sits down. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis
Ankylosing spondylitis	Typically, a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if female)
Peripheral arterial disease	Pain on walking, relieved by rest Absent or weak foot pulses and other signs of limb ischaemia Past history may include smoking and other vascular diseases

Wernicke's encephalopathy

Wernicke's encephalopathy: classic triad of:

- 1. nystagmus,
- 2. ophthalmoplegia
- 3. ataxia

Definition

 Wernicke's encephalopathy is a neuropsychiatric disorder caused by thiamine deficiency, which is most commonly seen in alcoholics.

Causes

- Most common: alcohol
- Rarer causes include:
 - ⇒ persistent vomiting,
 - ⇒ stomach cancer,
 - ⇒ dietary deficiency.

Features

- nystagmus (the most common ocular sign)
- ophthalmoplegia
- ataxia
- · confusion, altered GCS
- peripheral sensory neuropathy
- Sometimes bilateral wrist drop but more frequently bilateral foot drop with pain or pressure
 over the long nerves.

 petechial haemorrhages occur in a variety of structures in the brain including the mamillary bodies and ventricle walls

Investigations

- 1st investigations to order → therapeutic trial of parenteral thiamine
- · decreased red cell transketolase
- MRI

Treatment is with urgent replacement of thiamine (Pabrinex (Intravenous))

Korsakoff syndrome

Korsakoff's syndrome: Inability to acquire new memories and confabulation

Definition

• a late neuropsychiatric manifestation of Wernicke encephalopathy.

Pathophysiology

 alcohol → vitamin B1 (thiamine) deficiency → damage to <u>mammillary bodies</u> (structures of the limbic system)

Feature

- Wernicke's encephalopathy + antero- and retrograde amnesia and confabulation.
 - ⇒ confabulation (false memories) is a disturbance of memory, defined as the production of fabricated memories without the conscious intention to deceive.
 - ⇒ dementia is typically not reversible.

Investigations

• MRI finding → mammillary body degeneration

Treatment

• maintenance thiamine and rehabilitation

Anti-NMDA receptor encephalitis (Autoimmune encephalitis)

Definition

- It is a type of brain inflammation due to antibodies. (a paraneoplastic syndrome), presenting
 as prominent psychiatric features including agitation, hallucinations, delusions and
 disordered thinking; seizures, insomnia, dyskinesias and autonomic instability.
- might be misdiagnosed as a primary psychiatric illness.

Mechanism

 autoimmune with the primary target the N-methyl D-aspartate receptors (NMDAR) in the brain

Epidemiology

- 80% are female
- particularly prevalent in Afro-Caribbean patients.

Associations

Ovarian teratomas are detected in up to half of all female adult patients,

Investigations

- CSF
 - > can be normal initially.

- > may demonstrate pleocytosis
- > antibodies against NMDA receptors
- CSF titers of anti-NMDA receptor antibodies correlate with clinical illness
- MRI head
 - ⇒ can be normal in 50%
 - abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures.
- evaluation for an ovarian teratoma by MRI, CT scan, or ultrasound

Treatment

- immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination.
- · Resection of teratoma is also therapeutic.

CADASIL

Overview

- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
- A family history is almost always present, as it is an autosomal dominant condition, located to chromosome 19.
- · the most common genetic form of vascular dementia.

Features

- What is the pathophysiology of this condition?
 - ⇒ NOTCH3 mutation
- · strokes at a young age and
- early vascular (subcortical) dementia (multi-infarct dementia)
- · patients often present with migraine
- Recurrent ischaemic events (transient or permanent) & Severe mood disorders

Diagnosis

- Characteristic MRI changes include T2 weighted hyperintensity of the periventricular white matter
- DNA testing for the notch-3 gene mutation confirms the diagnosis.

Treatment

 the oral contraceptive pill should be stopped, given its association with stroke in migraine.

Myotonic dystrophy

Definition

 Myotonic dystrophy (also called dystrophia myotonica) is an inherited myopathy results in a selective atrophy of type I muscle fibers affects skeletal, cardiac and smooth muscle.

Genetics

 autosomal dominant, trinucleotide repeat disorder. Patients have between 50 to 1,000 CTG trinucleotide repeats in the myotonin protein kinase gene (normal is less than 30 repeats).

Types: There are two main types of myotonic dystrophy, DM1 and DM2.

	DM1	DM2
Genetics	DMPK (Dystrophia Myotonica-Protein	ZNF9 gene on chromosome 3
	Kinase) gene on chromosome 19	
Onset	Congenital, juvenile, or adult-onset	Adulthood
Features	Distal weakness more prominent	Proximal weakness more prominent
Severity	Sever disease	Mild disease

Features

- features developing at around 20-30 years old.
- myotonic facies (long, 'haggard' appearance), frontal balding, atrophy of temporalis, masseters and facial muscle, bilateral ptosis
- cataracts
- myotonia (tonic spasm of muscle), slow-relaxing grip may be noticed on initial hand-shake with the patient and is typical of myotonic dystrophy.
- weakness of arms and legs (distal initially)
- · mild mental impairment
- diabetes mellitus (Insulin resistance)
- testicular atrophy
- Dysarthric speech secondary to myotonia of the tongue and pharynx
- · cardiac involvement: heart block, cardiomyopathy
- dysphagia

Diagnosis

- Serology → increased serum CK
- \bullet $\;$ Electromyogram (EMG) \rightarrow the most appropriate next step to confirm the diagnosis
 - ⇒ EMG changes → Waxing and waning of potentials , termed the "dive bomber effect"
- Muscle biopsy
- · Genetic testing: the gold standard for confirming the diagnosis

Treatment: mostly symptomatic

- for weakness which is the main cause of disability \rightarrow there is no treatment
- for myotonia → phenytoin, quinine or procainamide may be useful, mexiletine is a <u>sodium</u> <u>channel</u> blocker often used for myotonic symptoms.
- for cardiac abnormalities → pacemaker
- for obstructive sleep apnea → CPAP
- Foot drop can be managed with → ankle-foot orthosis and splints.
- For ptosis: lid-lifting surgery has no place except in severe cases
- may need cataract extraction.
- Genetic counseling and testing

Prognosis

- The course is chronic progressive.
- Cardiac complications reduce life expectancy.

Top Tips

Dystrophia myotonica - DM1

- · distal weakness initially
- · autosomal dominant
- diabetes
- dysarthria



Dystrophinopathies

Overview

- X-linked recessive
 - ⇒ Affected father (Y, X):
 - All sons will not be affected and not carriers (His sons will get the X chromosome from their mother)
 - All his daughters will be carriers
 - ⇒ Carrier mother (X, X):
 - 50% of sons will be affected (there is a 1 in 2 chance (50:50) of passing the gene on to their sons.)
- due to mutation in the gene encoding dystrophin, dystrophin gene on Xp21

 dystrophin is a protein in muscle which connects the muscle membrane to actin, part of the muscle cytoskeleton

Diagnostic investigations

- 1st investigations to order
 - ⇒ serum CK
 - 50 to 100 times normal level consistent with Duchenne muscular dystrophy
 - ⇒ genetic testing
 - DNA analysis → Xp21 mutation → may present in both Duchenne and Becker muscular dystrophies
- Investigations to consider
 - ⇒ FMG
 - EMG can distinguish between neuropathic and myopathic pathology.
 - myopathic reading with fast firing, short duration but polyphasic and decreased amplitude motor units with early recruitment in the affected muscles
 - ⇒ muscle biopsv
 - absence of dystrophin → Duchenne muscular dystrophy
 - diminished quantity or quality of dystrophin → Becker muscular dystrophy

Duchenne muscular dystrophy (DMD)

- most common and most rapidly progressive muscular dystrophy
- there is a frameshift mutation resulting in one or both of the binding sites are lost leading to a severe form
- progressive proximal muscle weakness from 5 years
 - ⇒ Usually, there is severe progression with wheelchair dependence by the age of 12 on average
 - ⇒ Death usually occurs as a teenager or in the early 20s from respiratory failure.
- calf pseudohypertrophy
- Gower's sign: child uses arms to stand up from a squatted position
- intellectual impairment (30%)
- urinary and bowel incontinence (common)
- DMD patients tend to be hyperactive and have difficulty in focusing attention.

Becker muscular dystrophy

- there is a **non-frameshift insertion** in the dystrophin gene resulting in both binding sites being preserved leading to a **milder form**
- · develops after the age of 10 years
- Similar type of disease to Duchenne's, with a later onset (average age at presentation 12 years), milder phenotype and longer life expectancy
- intellectual impairment much less common
- Occasionally, patients present with CHF and cardiac arrhythmias before complaining of muscle weakness and before diagnosis.

Facio-scapulo-humeral muscular dystrophy (FSHMD)

- autosomal dominant form of muscular dystrophy.
- As the name suggests it is typically affects the face, scapula and upper arms first.
- Symptoms typically presents by the age of 20 years.
- · may go unrecognised until later life

 The presence of distal wasting and pes cavus (indicates a very chronic neuromuscular disorder with axonal loss)

Oculopharyngeal muscular dystrophy

- ptosis
- · weakness of the extraocular muscles
- dysphagia
- tongue atrophy

Foster-Kennedy syndrome

Foster Kennedy's syndrome is a combination of optic atrophy and central scotoma, contralateral papilloedema and anosmia.

Overview

- Foster-Kennedy syndrome describes a series of symptoms and signs associated with frontal lobe lesions.
- It is caused by optic and olfactory nerve compression and raised intracranial pressure.
- This is often secondary to a mass such as an olfactory groove meningioma.

Features

- · optic atrophy in the ipsilateral eye
- central scotoma in the ipsilateral eye
- · papilloedema in the contralateral eye
- anosmia
- symptoms of raised intracranial pressure such as nausea and vomiting,
- frontal symptoms such as emotional lability and memory loss.

The presence of optic atrophy on one side with contralateral papilloedema is characteristic of Foster Kennedy syndrome as it is usually due to frontal tumour or tumour within the olfactory bulb compressing the ipsilateral optic nerve and causing raised intracranial pressure.

Hypokalaemic periodic paralysis and thyrotoxic periodic paralysis

Epidemiology

- Most commonly seen in Asian men in their third to fifth decades
- The prevalence is much higher in patients with thyrotoxicosis of Chinese origin versus Caucasians, (13-14% vs. 0.1-0.2%).
- occurs in 10% of young Latin American or Asian men with thyrotoxicosis (of whatever aetiology).

Pathophysiology 1 4 1

- autosomal dominant disorder
- The underlying defect is a <u>mutation in muscle voltage-gated calcium channels</u>.
- Increase Na⁺/K⁺-ATPase activity → shift of potassium into tissues

Features

- **Episodes of paralysis:** sudden onset of complete weakness with speedy recovery.
 - ⇒ Attacks of focal or generalized flaccid muscle weakness (periodic paralysis)
 - ⇒ Proximal muscles are more prominently affected; respiratory and facial muscles are generally spared
 - ⇒ Variable duration (hours to days)
 - ⇒ Concomitant fatigue, muscle pain, and/or altered state of consciousness during the attacks
 - ⇒ Neurological examination is usually normal between attacks.
- Attacks may be precipitated by:
 - ⇒ Carbohydrate-rich meals
 - **⇒** Exercise
 - ⇒ Stress
- May associate with thyrotoxicosis
 - **⇒** With thyrotoxicosis called → Thyrotoxic hypokalaemic periodic paralysis
 - ⇒ Without thyrotoxicosis called → hypokalaemic periodic paralysis.

Diagnosis

- ↓ K+, documentation of hypokalaemia during an attack
- ↓ TSH, ↑ T3, T4 hormones (Thyrotoxic periodic paralysis)

Management

- Potassium infusion → provide immediate relief from symptoms
- · Continuous cardiac monitoring
- Lifelong potassium supplementation
- The periodic paralysis resolves when the thyrotoxicosis is treated.
- Non-selective beta-blocker such as propranolol blunts the hyperadrenergic stimulation of Na+/K+-ATPase and thus prevents intracellular shift of potassium and phosphate.

Neuromyelitis optica (NMO)

The classic antibody associated with neuromyelitis optica is NMO-IgG or antibodies against aquaporin-4.

Definition

demyelinating disease involving the optic nerves and spinal cord but sparing the brain.

Features

- monophasic or relapsing-remitting
- particularly prevalent in Asian populations
- Vomiting is also a common presenting complaint.

Diagnostic criteria: bilateral optic neuritis, transverse myelitis and 2 of the following 3 criteria:

- 1. Spinal cord lesion involving 3 or more spinal levels
- 2. Initially normal MRI brain
- 3. Aquaporin 4 positive serum antibody

Vertigo

Overview

- Vertigo is a sensation of spinning while you're actually stationary.
- Vertigo is caused most often by inner ear disease but can also be caused by disease of the vestibular nerve, brainstem, or cerebellum.
- Inner ear causes of vertigo include benign paroxysmal positional vertigo (BPPV), labyrinthitis, and Ménière disease.
- Horizontal-rotational nystagmus is associated with peripheral vertigo, whereas vertical nystagmus is associated with central vertigo.

Common causes of vertigo

Disorder	Notes
Labyrinthitis	 Recent viral infection or head trauma Sudden onset Nausea and vomiting Typically has associated tinnitus and a history of infection. Hearing may be affected
Vestibular neuritis	 Recent viral infection Recurrent vertigo attacks lasting hours or days No hearing loss
Benign paroxysmal positional vertigo	 Gradual onset Triggered by change in head position Each episode lasts 10-20 seconds
Meniere's disease	 Associated with hearing loss, tinnitus and sensation of fullness or pressure in one or both ears
Vertebrobasilar ischaemia	Elderly patientDizziness on extension of neck
Acoustic neuroma	 Hearing loss, vertigo, tinnitus Absent corneal reflex is important sign Associated with neurofibromatosis type 2

Distinguishing vertigo of brainstem and cerebellar ischemia from peripheral causes

The **HINTS** exam is a three-part, rapid beside oculomotor test used to help differentiate central from peripheral vertigo. **HINTS** stands for **Head Impulse**, **Nystagmus and Test of Skew**. The test consists of **three** parts:

- 1 Patients with peripheral vertigo will have abnormal (positive) head impulse testing, while patients with central vertigo typically have a normal (negative) head impulse test.
- 2 Patients with peripheral vertigo will have unidirectional, horizontal nystagmus, while patients with **central** vertigo can have **rotatory or vertical** nystagmus, or direction-changing horizontal nystagmus.
- **3** Alternate eye cover testing may reveal skew deviation in patients with central vertigo, and should be absent in peripheral vertigo.

Any of the following, whether present or untestable, suggest a brainstem or cerebellar lesion:

- Normal head impulse test on both sides
- Direction-changing nystagmus
- Skew deviation

The presence of all of the following suggests a peripheral lesion:

- · An abnormal head impulse test on one side
- Unidirectional, horizontal, torsional nystagmus that increases in intensity with gaze toward the fast phase
- Absent skew

The importance of these oculomotor tests is that brain imaging with either CT or MRI may be normal during the acute phase of ischemic symptoms. In this regard, the HINTS test appears to be more sensitive for the diagnosis of acute stroke than even brain MRI within the first two days after symptom onset

Benign paroxysmal positional vertigo (BPPV)

Overview

- vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards)
- · may be associated with nausea
- each episode typically lasts 10-20 seconds

Features

Vertigo and nausea, with nystagmus, fit best with benign paroxysmal positional vertigo, which occurs due to otolith detachment into the semicircular canals of the inner ear.

Diagnosis

- Positive Dix-Hallpike manoeuvre
 - ⇒ First-line test for suspected BPPV
 - ⇒ Positive Dix-Hallpike test: positional vertigo and nystagmus triggered during the maneuver
 - ⇒ Further steps for positive test: Perform Epley repositioning maneuver.

Treatment

- Symptomatic relief may be gained by Epley manoeuvre (successful in around 80% of cases)
- Medication is often prescribed (e.g. Betahistine) but it tends to be of limited value.

Prognosis

 BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months.

MRCPUK-part-1-May 2017 exam: H/O vertigo and dizziness precipitated by a change in head position. What is the most appropriate next step to confirm the diagnosis?

→ Dix-Hallpike manoeuvre

Meniere's disease

Definition

- Meniere's disease is a disorder of the inner ear of unknown cause.
- characterised by excessive pressure and progressive dilation of the endolymphatic system.

Epidemiology

- more common in middle-aged adults but may be seen at any age.
- similar prevalence in both men and women.

Features

- Recurrent episodes of vertigo, (the prominent symptom)
- Tinnitus and hearing loss (sensorineural).
- · Sensation of aural fullness or pressure
- Nystagmus
- · Positive Romberg test
- · Episodes last minutes to hours
- Typically, symptoms are unilateral but bilateral symptoms may develop after a number of years

Natural history

- symptoms resolve in the majority of patients after 5-10 years
- the majority of patients will be left with a degree of hearing loss
- psychological distress is common

Management

- patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- · Acute attacks: buccal or intramuscular prochlorperazine.
- Restriction of salt and fluid may hasten resolution.

MRCPUK-part-1-May 2013 exam: H/O recurrent attacks of 'dizziness' + 'roaring' sensation in the left ear. Weber's test localises to the right ear. What is the most likely diagnosis?

→ Meniere's disease

Vestibular neuronitis

Definition

Vestibular neuronitis is a cause of vertigo that often develops following a viral infection.

Features

- · recurrent vertigo attacks lasting hours or days
- nausea and vomiting may be present
- · horizontal nystagmus is usually present
- · no hearing loss or tinnitus

Management

- vestibular rehabilitation exercises are the preferred treatment for patients who experience chronic symptoms
- betahistine is often used although the evidence base suggests it is less effective than vestibular rehabilitation

Tinnitus

Causes of tinnitus

Meniere's disease	Associated with hearing loss, vertigo, tinnitus and sensation of fullness or pressure in one or both ears	
Otosclerosis	 Onset is usually at 20-40 years Conductive deafness Tinnitus Normal tympanic membrane (10% of patients may have a 'flamingo tinge', caused by hyperaemia) Positive family history 	
Acoustic neuroma	 Hearing loss, vertigo, tinnitus Absent corneal reflex is important sign Associated with neurofibromatosis type 2 	
Hearing loss	Causes include excessive loud noise and presbycusis	
Drugs	 Aspirin Aminoglycosides Loop diuretics Quinine 	

The combination of sensorineural deafness, facial nerve palsy and cranial nerve V involvement suggests a cerebellopontine angle tumour, for example, acoustic neuroma.

Other causes include

- impacted ear wax
- chronic suppurative otitis media

Clinical physiology of the ear

- The scala media contains the organ of Corti, which produces nerve impulses in response to sound vibrations.
- High-frequency waves are detected in the scala vestibuli.
- Low-frequency waves are detected in the scala tympani.
- Normal hearing frequency ranges from 20 to 20 000 Hz.

Hearing loss

	Conductive hearing loss	Sensorineural hearing loss
Age of Onset	commonly in childhood or young adulthood	commonly in middle or late age
Aetiology	 Otosclerosis Otitis media Ear barotrauma Cerumen Impaction External auditory canal atresia 	 Ménière's disease Acoustic neuroma Noise-induced hearing loss Internal ear infections Presbycusis
Pathophysiology	External or middle ear pathology that disrupts conduction of sound into the inner ear	Inner ear, cochlear, or auditory nerve pathology that impairs neuronal transmission to the brain
Clinical Features	 Hearing improves in noisy environments Volume of voice remains normal because inner ear and auditory nerve are intact Sound normally is not distorted Features of external auditory canal pathology (e.g., cerumen impaction) 	 Hearing worsens in noisy environments Volume of voice may be loud because nerve transmissions are impaired Tend to lose higher frequencies preferentially, such that sounds may be distorted Absent features of external auditory canal pathology
Weber Test(unilateral hearing loss)	Lateralization to impaired ear (cannot hear ambient room noise well, so detection of vibration is greater)	Lateralization to good ear (sound is not transmitted by damage inner ear or auditory nerve)
Rinne Test(unilateral hearing loss)	Bone conduction > air conduction (vibrations bypass blockage to reach the cochlea)	Air conduction > bone conduction (the inner ear or auditory nerve cannot transmit sound information well regardless of how vibrations reach the cochlea)

Down syndrome: Hearing loss

- 60%-70 develop conductive deafness due to glue ear
- 10%-15% develop sensorineural deafness

Rinne's and Weber's test

- Performing both Rinne's and Weber's test allows differentiation of conductive and sensorineural deafness.
- Rinne's test
 - tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus
 - ⇒ air conduction (AC) is normally better than bone conduction (BC)
 - ⇒ if BC > AC then conductive deafness
- Weber's test
 - ⇒ tuning fork is placed in the middle of the forehead equidistant from the patient's ears
 - ⇒ the patient is then asked which side is loudest
 - ⇒ in unilateral sensorineural deafness, sound is localised to the unaffected side
 - ⇒ in unilateral conductive deafness, sound is localised to the affected side

Motion sickness

Motion sickness - hyoscine > cyclizine > promethazine

Overview

 Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement

Management

- the BNF recommends hyoscine (e.g. transdermal patch) as being the most effective treatment.
 - ⇒ Use is limited due to side-effects
- non-sedating antihistamines such as cyclizine or cinnarizine are recommended in preference to sedating preparation such as promethazine

Peripheral neuropathy

Definitions

- Allodynia: pain caused by a stimulus that does not normally cause pain (e.g. light touch, contact with clothing)
- Dysesthesia: abnormal spontaneous sensations (burning, stinging, stabbing) from activities that do not normally cause pain)
- Paresthesia: an abnormal skin sensation in the absence of a stimulus (described as burning, prickling, itching, tingling)
- Hyperesthesia: increased sensitivity to sensory stimuli
- **Hypoesthesia**: decreased sensitivity to sensory stimuli

Classifications

- neuropathy is classified into:
 - ⇒ mononeuropathy commonly due to entrapment or trauma;
 - ⇒ mononeuropathy multiplex commonly due to leprosy and vasculitis; and
 - ⇒ polyneuropathy due to systemic, metabolic or toxic etiology.
- Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss	Predominately sensory loss
Guillain-Barre syndrome	diabetes
 porphyria 	uraemia
 lead poisoning 	 leprosy
 hereditary sensorimotor neuropathies 	 alcoholism
(HSMN) - Charcot-Marie-Tooth	 vitamin B12 deficiency
 chronic inflammatory demyelinating 	 amyloidosis
polyneuropathy (CIDP)	Sjogren's syndrome
diphtheria	

Types

Large-fibre neuropathy

- ⇒ the earliest clinically identifiable feature of peripheral sensory motor neuropathy.
- ⇒ Reduced light pressure sensation and vibration sensation are the earliest clinically identifiable manifestations of large fibre neuropathy.
- ⇒ Features
 - paraesthesia
 - glove and stocking sensory loss
 - increased risk of charcot arthropathy, particularly in association with autonomic nerve dysfunction.
 - reduced vibration and proprioception sensation,
 - loss of reflexes (diminished ankle jerks),
 - muscle wasting
 - increased blood flow.

Small-fibre neuropathy

- typically presents with pain and loss of temperature sensation, with relative preservation of other sensory modalities and muscle strength.
 - General neurological examination and reflexes are usually normal
- → not detectable on conventional nerve conduction studies, which can only investigate large fibres.
- - Diabetes
 - is a common cause and should be excluded in any patient with a painful peripheral neuropathy.
 - Conditions in which the small fibres are preferentially affected in the early stages include diabetes and amyloidosis. In the later stages however the neuropathy in these conditions also affects large fibres.
 - Amyloidosis
 - Fabry's disease
 - X-linked lysosomal storage disorder
 - causes a painful peripheral neuropathy, due to deposition of glycosphingolipids within small sensory fibres.
 - Nerve conduction studies are typically normal as large fibres are unaffected.
 - Tangier's disease
 - Hereditary sensory and autonomic neuropathy
 - Sjogren's syndrome: pure sensory neuropathy (ganglionopathy).
 - Chronic idiopathic small fiber sensory neuropathy

Small-fibre neuropathy	Large-fibre neuropathy
Loss of pain and temperature	Loss of touch, vibration and position sense
	Sensory ataxia
Preservation of reflexes and motor function	Reflexes lost early and motor functions impaired
Electrophysiological test is silent	Impaired nerve conduction velocity
Skin biopsy are used	

Biopsy in diagnosis of neuropathy

- Skin punch biopsy can be done if a small-fiber neuropathy is suspected; loss of nerve endings supports that diagnosis.
- Nerve biopsy is occasionally done to help differentiate demyelinating from vasculitic largefiber neuropathies.
- If vasculitis is a consideration, the biopsy specimen should include skin and muscle to increase the likelihood of a definitive diagnosis.
- ⇒ If all limbs are affected, MRI can be done to rule out cervical spinal cord compression.

Lead neuropathy

purely motor neuropathy affecting mainly the upper limbs.

Thalamic infarcts neuropathy

- commonly cause late-onset of severe neuropathic pain weeks to months after the stroke.
- The pain is intractable to analgesics.
- The treatment of choice for neuropathic pain is amitriptyline/gabapentin.

Alcoholic neuropathy

Epidemiology

 Alcohol abuse and diabetes are the commonest causes of peripheral neuropathy in the United Kingdom.

Pathophysiology

- Typically, all fibre types are affected and it is seen with a higher alcohol consumption more than 30 units.
- · affects mainly the spinothalamic pathway.
- secondary to both direct toxic effects and reduced absorption of B vitamins (thiamine deficiency)

Features

- slowly progressive
- sensory symptoms typically present prior to motor symptoms
- Pain is usually a more dominant feature

Treatment

thiamine and cessation of alcohol use

Peripheral neuropathy: axonal vs. demyelinating

Peripheral neuropathy	Causes	Nerve conduction studies (NCS)
Axonal	alcohol isoniazid Simvastatin Diabetes mellitus* vasculitis vitamin B12 deficiency* Renal failure hereditary sensorimotor neuropathies (HSMN) type II (*may also cause a demyelinating picture)	 normal conduction velocity reduced amplitude
Demyelinating	Guillain-Barre syndrome chronic inflammatory demyelinating polyneuropathy (CIDP) Paraproteinaemia Amiodarone (Amiodarone can cause a mixed demyelinating and axonal picture) Refsum's disease hereditary sensorimotor neuropathies (HSMN) type I (Charcot-Marie-Tooth disease) Leukodystrophies.	reduced conduction velocity normal amplitude

- Nerve conduction studies (NCS) are useful in determining between axonal and demyelinating pathology
- Segmental demyelination is a feature seen in axons in the central nervous system with **multiple sclerosis**.

Wallerian degeneration

- Wallerian degeneration is degeneration of the portion of the nerve distal to the injury.
- It occurs following axonal injury in both the peripheral and central nervous systems
- usually begins within 24-36 hours of injury.

Electromyogram (EMG)

 A pattern of rapidly recruited low amplitude short duration motor units on the electromyogram (EMG) would be considered to represent myopathic changes rather than de-innervation.

Drugs causing peripheral neuropathy

- Antibiotics: nitrofurantoin, metronidazole
- Amiodarone
- Isoniazid
- Vincristine
- Tricyclic antidepressants

Critical illness polyneuropathy

- Prolonged periods in the Intensive Therapy Unit, irrespective of the underlying pathology, are associated with a risk of developing critical illness polyneuropathy
- It is an axonal neuropathy and thus muscle wasting may occur
- May be predominantly sensory, predominantly motor or mixed

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barre syndrome (hyporeflexia or areflexia, paraesthesia and mild sensory deficits in the upper and lower extremities, weakness) except that it follows a chronic progressive course.

Overview

- CIDP is characterised by progressive weakness and impaired sensory function in the upper and lower limbs.
- **subacute** sensory and motor peripheral neuropathy
- The cause of the demyelination is not understood.
- More common in young adults and in men.
- mainly causes motor impairment (distal and proximal).
- CIDP causes a large fibre peripheral neuropathy (Joint position sense and vibration are carried through large fibres)

Features

- weakness of the limbs
- areflexia
- abnormal sensation (which typically begins distally)
- fatique.
- Autoantibodies against GM1 gangliosides

Differential diagnosis

- 1. CIDP is closely linked to **Guillain-Barré syndrome (GBS**), and is thought by some to be its chronic counterpart.
 - ⇒ Both CIDP and GBS can affect motor and sensory nerves
 - ⇒ (GBS) is an <u>acute</u> (which reaches its peak in severity <u>within six weeks</u>), postinfectious neuropathy
 - ⇒ Whereas CIDP is subacute (several months history)
- 2. **Hereditary motor and sensory neuropathy (HMSN)** is normally a **very chronic** neuropathy developing **over many years** and usually with a family history of the condition.

Treatment

- Corticosteroids
- plasmapheresis
- Intravenous immunoglobulin
- Physiotherapy

Diabetic neuropathy(see endocrinology system)

Neuropathic pain

Definition

- neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system.
- It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- · diabetic neuropathy
- post-herpetic neuralgia
- · trigeminal neuralgia
- · prolapsed intervertebral disc

Management of neuropathic pain

- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
 - ⇒ please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- · pain management clinics may be useful in patients with resistant problems

January 2019 exam: severe 'shooting' pains after blistering rash. What is the most appropriate next step in management? Amitriptyline

Autonomic neuropathy

Features

- impotence, inability to sweat, postural hypotension
- postural hypotension e.g. drop of 30/15 mmHg
- loss of decrease in heart rate following deep breathing
- pupils: dilates following adrenaline instillation

Causes

- diabetes
- Guillain-Barre syndrome
- multisystem atrophy (MSA), Shy-Drager syndrome
- · Parkinson's
- infections: HIV, Chagas' disease, neurosyphilis
- drugs: antihypertensives, tricyclics
- craniopharyngioma

<u>Hereditary sensorimotor neuropathy (HSMN)</u> (Charcot-Marie-Tooth disease)

Mixed motor and sensory symptoms, slowly progressing initially in the lower limbs and then to the upper limbs, together with a family history suggests a diagnosis of Hereditary sensorimotor neuropathy (HSMN)

Definition

- hereditary nerve disorders with defective production of peripheral myelin protein-22 which is involved in the structure and function of the myelin sheath.
- Charcot-Marie-Tooth disease is the most commonly inherited neurological disorder,

Genetics

- autosomal dominant
- caused by deletion in the <u>PMP22 gene</u>, the same gene mutation responsible for hereditary neuropathy with liability to pressure palsies.
- Common <u>peroneal nerve</u> is the most commonly affected nerve (36%) followed by the ulnar nerve (28%).

Types

- HSMN type I
 - ⇒ the most common form
 - ⇒ primarily due to demyelinating pathology
 - hence C fibres are not affected, as they are unmyelinated.
 - Which nerve fibers are relatively preserved in this patient?
 - C fibers
 - ⇒ due to defect in PMP-22 gene (which codes for myelin)
 - ⇒ loss of myelin in peripheral neurons
 - ⇒ features often start at puberty
 - ⇒ motor symptoms predominate
 - ⇒ distal muscle wasting, pes cavus, clawed toes
 - ⇒ foot drop, leg weakness often first features
- HSMN type 2
 - ⇒ primarily due to axonal pathology
 - ⇒ loss of peripheral neurone themselves

Features

- motor and sensory deficits.
- · early weakness of the distal muscles of the limbs.
- scoliosis
- pes cavus
 - ⇒ a deformity of the foot involving high arches, muscle wasting and clawed toes.

Diagnosis

- neurophysiology: Electromyography (EMG) and nerve conduction studies (NCS) may distinguish between the demyelinating (type 1) and axonal (type 2) forms.
- Diagnosis confirmed by genetic testing.
- Nerve biopsy, usually the sural nerve, will demonstrate "onion-bulb" formations due to continual remyelination and demyelination of peripheral nerves.

Management

The mainstay of the management is physical therapy.

Prognosis

· Life expectancy is normal.

MRCPUK-part-1-September 2017 exam: A woman with Charcot-Marie-Tooth disease (type 1), how likely her children will get the disease?

→ 50% (autosomal dominant)

Mononeuritis multiplex

Definition: ≥ 2 isolated mononeuropathies

Causes

Axonal injury caused by damage to vasa nervorum

 Occurs in conditions characterized by the development of granulomas and/or microangiopathy (e.g., diabetes mellitus, rheumatoid arthritis, vasculitides, SLE, Lyme disease, amyloidosis, HIV, polyarteritis nodosa)

Features: painful, asymmetrical sensory and motor symptoms

Diagnosis: Nerve biopsy should be performed to confirm the diagnosis

Treatment: includes prednisolone and cyclophosphamide

Refsum's disease

Overview

- · autosomal recessive disorder
- caused by defective alpha oxidation of phytanic acid leading to its accumulation in tissues.
- Phytanic acid is present in a wide variety of foods including dairy products, fish, beef and lamb.
- The onset of the disease is normally in the late teens or 20s.

Features

- sensorimotor peripheral neuropathy
- sensorineural deafness.
- anosmia.
- · cerebellar ataxia
- pes cavus.
- Night blindness and visual problems occur secondary to retinitis pigmentosa.
- Cardiac conduction abnormalities and cardiomyopathies may also occur.
- Epiphyseal dysplasia causes a characteristic shortening of the fourth toe.
- Serum phytanic acid levels are elevated.

Treatment

· dietary restriction of foods containing phytanic acid.

Vasculitic neuropathy

Overview

- The presence of nail fold infarcts and the multifocal nature of the neuropathy indicate that a vasculitic cause is most likely
- Hepatitis C infection may be associated with cryoglobulinaemia, which causes a vasculitic syndrome including neuropathy

Other conditions associated with vasculitic neuropathy include

- Polyarteritis nodosa
- Churg-Strauss syndrome
- · rheumatoid arthritis
- · systemic lupus erythematosus
- systemic sclerosis
- Wegener's granulomatosis

Treatment include one or several of the following

- high-dose intravenous steroids
- plasma exchange
- intravenous immunoglobulins

Guillain-Barre syndrome

FVC is used to monitor respiratory function in Guillain-Barre syndrome

• also known as Post-infectious polyradiculopathy

Definition

- Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection :
 - ⇒ classically Campylobacter jejuni
 - ⇒ cytomegalovirus

Pathogenesis

- cross reaction of antibodies with gangliosides in the peripheral nervous system
- correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated
- anti-GM1 antibodies in 25% of patients

Features

· characteristic features

- ⇒ progressive weakness of all four limbs. The weakness is classically ascending i.e. the lower extremities are affected first, however it tends to affect proximal muscles earlier than the distal ones.
- ⇒ Sensory symptoms tend to be mild (e.g. distal paraesthesia) with very few sensory signs. However, a sensory level is NOT a feature and would suggest cervical myelopathy
- ⇒ symmetrical involvement is typical, asymmetry present in only 9% of patients.
- ⇒ Some patients experience back pain in the initial stages of the illness.

Other features

- ⇒ areflexia
- ⇒ cranial nerve involvement e.g. diplopia
- ⇒ autonomic involvement: e.g. urinary retention
- ⇒ Muscle wasting is typical with prolonged illness.
- Bulbar involvement occurs in 50%, with a risk of aspiration and respiratory insufficiency
- ⇒ urinary incontinence or retention (in 20% of cases).

Less common findings

⇒ papilloedema: thought to be secondary to reduced CSF resorption

Investigations

- CSF analysis
 - ⇒ elevated protein, with normal glucose and <u>no pleocytosis</u>.
 - ⇒ a rise in CSF protein doesn't peak until the second or third week of the illness.
 - ⇒ CSF cell counts are usually within normal limits,
- <u>Nerve conduction studies</u> (including F waves for the proximal spinal root, looking for widespread demyelination)
- MRI may be indicated to rule out spinal cord lesions, peripheral neuropathies and neuromuscular junction disorders.

Management

- IV immunoglobulins (IVIG):
 - **⇒** First line therapy.
 - ⇒ as effective as plasma exchange. No benefit in combining both treatments.
 - ⇒ IVIG may be easier to administer and tends to have fewer side-effects
- plasma exchange
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function .
 - ⇒ FVC of less than 1 litre would be an indication for immediate ventilation
 - ⇒ Forced vital capacity of 1.4 L is most likely to predict the need for invasive ventilation
 - ⇒ FVC of less than 15ml/kg (or less than 30% of FVC predicted) or a rising PaCO₂ are indications for mechanical ventilation.

Prognosis

- 20% suffer permanent disability, 5% die
- Poor prognostic features
 - ⇒ age > 40 years
 - ⇒ poor upper extremity muscle strength
 - previous history of a diarrhoeal illness (specifically Campylobacter jejuni)
 - ⇒ high anti-GM1 antibody titre
 - ⇒ need for ventilatory support
 - ⇒ There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome

MRCPUK-part-1-January 2008 exam: Regarding nerve conduction studies for suspected Guillain-Barre syndrome. Which finding would be most consistent with this diagnosis? Reduced conduction velocity

MRCPUK-part-1-May 2019 exam: a patient developed weakness in his legs extended to his arms after viral illness. ↓↓ power, reflexes and sensation in his lower limbs. Developed SOB &↓↓ (FVC). Given the likely diagnosis, what is the treatment of choice? Intravenous immunoglobulin

(Guillain-Barre syndrome (GBS) secondary to a viral illness, possibly the **Epstein-Barr virus**)

MRCPUK-part-1-May 2020 exam: H/O double vision & ↓↓ eye movement + unsteadiness + ↓↓ reflexes + past-pointing. What is the most likely diagnosis? Miller Fisher syndrome

Miller Fisher syndrome

- areflexia, ataxia, ophthalmoplegia
- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. The eye muscles are typically affected first
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- anti-GQ1b antibodies are present in 90% of cases

DVLA: neurological disorders

DVLA advice post CVA: cannot drive for 1 month

DVLA advice post multipler TIAs: cannot drive for 3 months

- The guidelines below relate to car/motorcycle use unless specifically stated.
- For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- First seizure: 6 months off driving*.
 - ⇒ *previously rule was 12 months. It is now 6 months off driving if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicated
- For patients with established epilepsy they must be fit free for 12 months before being able to drive
- Stroke or TIA: 1 month off driving
- Multiple TIAs over short period of times: 3 months off driving
- Craniotomy e.g. For meningioma: 1 year off driving
 - ⇒ if the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free
- Pituitary tumour:
 - ⇒ craniotomy: 6 months:
 - ⇒ trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- Glioblastoma
 - ⇒ A patient with a high-grade glioma (that is, WHO grade 3 or 4) such as a glioblastoma will be unable to drive for at least two years following completion of treatment.
 - After the two years have elapsed the DVLA will consult with the physicians involved in the patient's care and a decision is made regarding return of the licence.
- Brain metastases
 - ⇒ solitary metastatic deposit that is fully excised would be considered for a licence one year after primary treatment if free from recurrence and no evidence of secondary spread elsewhere.

- ➡ multiple metastases would require at least two years off driving from time of completion of treatment. After the two years have elapsed the DVLA will consult with the physicians involved in the patient's care and a decision is made regarding return of the licence.
- · Narcolepsy/cataplexy:
 - ⇒ cease driving on diagnosis,
 - ⇒ can restart once 'satisfactory control of symptoms'
- Chronic neurological disorders e.g. multiple sclerosis, motor neuron disease:
 - ⇒ DVLA should be informed,
 - ⇒ complete PK1 form (application for driving licence holders state of health)
- Syncope
 - ⇒ simple faint: no restriction
 - ⇒ single episode explained and treated: 4 weeks off
 - ⇒ single episode, unexplained: 6 months off
 - ⇒ two or more episodes: 12 months off

DVLA regulations: for seizure and stroke

Case	Group 1 Car & motorcycle	Group 2 Bus and lorry
First epileptic seizure/isolate d seizure	no driving for 6 months.	no driving for 5 years.
Epilepsy or multiple seizures	no driving for 12 months.	must remain seizure-free for 10 years (without epilepsy medication)
Dissociative seizures	no driving for 3 months after event free.	no driving for 3 months after event free.
Withdrawal of epilepsy medication	no driving for 6 months after the last dose.	must remain seizure-free for 10 years (without epilepsy medication).(no special considerations for withdrawal)
Single TIA, Stroke	no driving for 1 month.	no driving for 1 year.
Multiple TIA	no driving for 3 months.	no driving for 1 year.

Susac syndrome

- Susac syndrome presents with the triad of:
 - **⇒ Encephalopathy**
 - **⇒** branch retinal artery occlusion
 - ⇒ and hearing loss
- Due to involvement of the pre-capillary arterioles of the brain, retina and cochlea.

Altitude related disorders

Types

- There are three main types of altitude related disorders:
- All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes
 - 1. acute mountain sickness (AMS),
 - **Features** of AMS start to occur above 2,500 3,000m.
 - developing gradually over 6-12 hours and potentially last a number of days
 - ❖ headache
 - nausea
 - fatigue
 - Prevention and treatment of AMS
 - the risk of AMS may actually be positively correlated to physical fitness
 - gain altitude at no more than 500 m per day
 - acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
 - Treatment:
 - Descent
 - generally a self-limiting condition.

2. high altitude pulmonary edema (HAPE)

- A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE)
- potentially fatal conditions
- HAPE presents with classical pulmonary oedema features
- Management of HAPE
 - descent
 - nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors
 - ⇒ All seem to work by reducing systolic pulmonary artery pressure
 - oxygen if available

3. high altitude cerebral edema (HACE).

- A minority of people above 4,000m go onto develop high altitude cerebral oedema (HACE),
- potentially fatal conditions
- HACE presents with headache, ataxia, papilloedema
- Management of HACE
 - descent
 - dexamethasone

Complex regional pain syndrome (CRPS)

- (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia.
- (CRPS) is a chronic pain condition that can affect any area of the body, but often affects an
 arm or a leg, and occurs after an injury or rarely after a sudden illness such as a heart
 attack or stroke.
 - ⇒ typically occur following surgery or a minor injury.
- The condition can sometimes appear without obvious injury to the affected limb.
- 3 times more common in women.

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• CRPS may have three stages (acute, dystrophic, and atrophic), with variable progression from one stage to another.

There are two types of CRPS:

- type I (most common): there is no demonstrable lesion to a major nerve
- type II: there is a lesion to a major nerve

Character of the pain

- intense and burning
- disproportionate to the original injury
- · worse over time
- · Spreads beyond the site of injury and
- associated with hyperalgesia, hyperpathia or allodynia on examination. These features do not occur in DVT, osteomyelitis, or cellulitis.

Features

- · progressive, disproportionate symptoms to the original injury/surgery
- allodynia
- · temperature and skin colour changes
- · oedema and sweating
- motor dysfunction
- · the Budapest Diagnostic Criteria are commonly used in the UK

Diagnosis

- · clinical diagnosis
- Plain radiographs may show soft tissue swelling, peri-articular osteoporosis, and rarely
 erosions
- MRI may also show bone marrow oedema apart from these changes
 - ⇒ In the atrophic phase, imaging may show contractures.
- 99mTc bone scan shows hypervascularity in the acute phase, and hypovascularity in the

Management

- early physiotherapy is important
- neuropathic analgesia in-line with NICE guidelines
- specialist management (e.g. Pain team) is required

Dystonia

Definition:

involuntary sustained or spasmodic muscle contractions

Types

Focal dystonias

- ⇒ Involves a single body part
- ⇒ Cervical dystonia, or torticollis, is the most common focal dystonia.
- ⇒ In 20-30% of patients, focal dystonias become segmental or multifocal.
- ⇒ <u>Blepharospasm</u> is a type of dystonia described as a sustained eyelid twitch.
 - It is associated with stress, lack of sleep, nutrition, and strain.
- ⇒ writer's cramp dystonia or musician's dystonia
 - A common upper limb dystonia
 - This task-specific dystonia, manifesting as hyperextension or hyperflexion of the wrist and fingers, → unable to write
 - may be triggered by repetitive activities such as writing and attempting to play the piano or other musical instruments.

- often relieved by a geste antagoniste, in which palpation of another unaffected part of the body leads to relief of symptoms, thought to be a result of alternative sensory input to cortical networks with altered plasticity.
- Segmental dystonia
 - ⇒ Affects 2 or more contiguous regions of the body
- Multifocal dystonia
 - ⇔ Consists of abnormalities in noncontiguous body parts
- · Generalised dystonias,
 - ⇒ involve a greater number of muscle groups.
 - ⇒ involves the trunk and limbs.

Treatment

 Benztropine is an anti-cholinergic drug that is used in the treatment of Parkinson's disease, Parkinsonism, and acute dystonia.

Cervical dystonia (torticollis)

- The term torticollis is derived from the Latin words tortus for twisted neck
- Torticollis is a fixed or dynamic tilt, rotation, or flexion of the head and/or neck.
- involuntary neck movements
- commonly affects women
- Secondary causes need to be excluded such as drugs (eg neuroleptics) and cervical spine abnormalities
- . Botulinum toxin injection is the first-line treatment for cervical dystonia (torticollis)

Botulism

Descending weakness with autonomic dysfunction (fixed dilated pupils) is typical of botulism.

Definition

• Botulism is a neurological disorder caused by Clostridium botulinum and is characterized by flaccid paralysis due to inhibition of acetylcholine release at the neuromuscular junction.

Features

- The clinical presentation of descending weakness with autonomic dysfunction (fixed dilated pupils) is typical of botulism.
- Typical initial features include:
 - ⇒ Diplopia
 - ⇒ Ptosis
 - ⇒ Facial weakness
 - ⇒ Dysarthria, and
 - ⇒ Dysphagia.
- Later, respiratory difficulty and limb weakness occur.
- impaired cholinergic transmission also involves **autonomic** synapses, causing poorly reactive dilated pupils, dry mouth, paralytic ileus and occasionally bradycardia.
- · Reflexes are depressed or absent.

Investigations

- It is a neuromuscular junction disorder and therefore nerve conduction studies and EMG are normal.
- Cerebrospinal fluid analysis is usually normal.
- Repetitive nerve stimulation shows incremental responses, which is diagnostic of botulism.
- sensation is normal

Treatment

Heptavalent antitoxin is the most appropriate therapy

Botulinum toxin

- Botulinum toxin is produced by Clostridium botulinum, a Gram-positive, sporeforming, obligate anaerobe
- Botulinum toxin type A (or trade name Botox®)

Action

- block acetylcholine release at the neuromuscular junction and so to produce muscle weakness.
- myasthenia gravis would be expected to worsen with this treatment

Indications

- Botulinum toxin is the treatment of choice for focal dystonia (such as torticollis, and hemi-facial spasm) and focal dystonia.
- Botulinum toxin injections are also used in patients with:
 - ⇒ hemifacial spasm
 - ⇒ blepharospasm
 - ⇒ spasticity
 - spasticity associated with stroke
 - spasticity associated with cerebral palsy
 - ⇒ Primary axillary hyperhidrosis
 - ⇒ Strabismus
 - ⇒ Cervical dystonia.

Side effects

- Occasionally systemic absorption of the toxin can affect distal muscles causing symptoms such as diplopia and dysphagia.
- The main side-effect is excessive weakness in the treated muscle

Contra-indications

- · myasthenia gravis
- other generalised muscle conditions

Paraneoplastic cerebellum syndrome

The patient with progressive ataxia and dysarthria following malignancy

Causes

 Associated malignancies are lung cancer (usually with small cell lung carcinoma), breast cancer, ovarian cancer and lymphoma

Features

• include ataxia, dysarthria, vertigo, oscillopsia, nystagmus and dysmetria

Investigations

• Brain imaging and CSF analysis are either normal or show non-specific changes

- antibodies
 - ⇒ anti-Hu antibody (a type of antineuronal antibody)
 - ⇒ anti-Purkinje-cell antibodies
- CT chest, abdomen and pelvis and mammogram are required to look for a primary neoplasm.
- A whole body positron emission tomography (PET) scan is preferable but not widely available.

Treatment

Occasionally patients respond to steroids, immunoglobulins or plasmapheresis.

Lumbosacral plexopathy

The patient presents with generalised weakness of the right leg associated with pelvic pain, leg oedema and autonomic dysfunction. The most likely diagnosis is a lumbosacral plexopathy.

Overview

- Anatomically, the lumbosacral plexus consists of lumbar (L1-L4) and sacral (S1-S5) portions.
- **Upper: lumbar plexus** lesion will cause weakness of hip flexion and adduction of the thigh and extension of the leg with anaesthesia over the anterior thigh and leg.
- Lower: sacral plexus lesions will weaken the posterior thigh and foot muscles.
- Lesions affecting the entire plexus will affect all muscle groups causing weakness or
 paralysis of the leg, areflexia and anaesthesia from the toes, to involve the perianal area.

Causes

- Trauma: Posterior hip dislocation, Sacral fracture
- Metabolic, inflammatory, and autoimmune causes: DM (diabetic amyotrophy), Amyloidosis, Sarcoidosis
- Infections and local abscess (e.g. vertebral osteomyelitis, tuberculosis, fungal infections, psoas abscess)
- Radiation therapy of the abdominal and pelvic malignancies.
- Pregnancy-related: Mostly occur in the third trimester and after delivery due to birth trauma.
- Damage to the vasculature innervating the LS plexus: femoral vessel catheterization

Epidemiology

 More common in women due to the predisposing risk factors of pregnancy and gynecological cancers.

Pathophysiology

- Direct injury, compression or traction on the plexus (Trauma, tumor, hematoma
- Microvascular injury and ischemic damage (Radiation)
- Inflammatory or microvascular changes (Diabetic and non-diabetic)

Features

- Low back pain radiating to one side.
 - ⇒ Pain may be positional, worse in a supine position.
 - ⇒ Patients with diabetic LS plexopathy (diabetic amyotrophy) typically complain of unilateral pain in the proximal thigh.
 - ⇒ lumbosacral plexopathy secondary to radiotherapy is usually painless.

- Muscle weakness and atrophy may occur in severe cases.
- A straight leg raise test is positive in more than half of the patients.
- Knee jerk reflex is affected in lumbar plexopathy and ankle jerk is affected in sacral plexopathy.
- Muscle weakness in hip flexion, knee extension, or adduction suggests a possible injury to the lumbar plexus.
- Sensory changes ((numbness, paresthesias, dysesthesias (painful sensations elicited by nonpainful cutaneous stimuli, e.g., light touch)).
 - ⇒ Medial thigh, anterior thigh, and medial suggest lumbar plexus involvement
 - ⇒ Posterior thigh, dorsum of the foot, and perineum suggest sacral plexus involvement.

A history of a road traffic accident, abdominopelvic neoplasm, radiotherapy, abdominal surgery, diabetes mellitus, bleeding disorders, or recent pregnancy hints towards lumbosacral plexopathy and narrows down the etiology.

Radiation plexopathy can often present without pain, only weakness and sensory changes. Unlike other types of plexopathy, it is usually bilateral and can occur even years after radiation.

Diagnosis

- MRI with gadolinium contrast is the best test for the evaluation of the LS plexus.
- When there are contraindications to MRI (e.g., a noncompatible pacemaker), a computed tomography (CT) scan with contrast can be utilized.
- Electromyography (EMG) differentiate lumbosacral plexopathy from other types of neuropathy or radiculopathies.
 - ⇒ Denervation of the paraspinal muscles is commonly seen in radiculopathy and helps to differentiate from lumbosacral plexopathy.

Treatment

- · Treatment of underline cause: e.g. relieve of compression
- Symptomatic treatment with analgesics and muscle relaxants:
 - ⇒ Compression: NSAIDs, opioids
 - ⇒ Neuropathic pain: pregabalin, gabapentin, duloxetine, amitriptyline
 - ⇒ Diabetic amyotrophy is a transient condition that usually resolves with good glycemic control.
- For radiation-induced plexopathy: there are no known treatments, physiotherapy and rehabilitation are the mainstays of treatment. Further radiotherapy sessions should be discontinued.

Cervical roots

Root	Dermatome distribution	Myotome distribution	Tendon reflex
C2	Posterior half of the skull (cap)	-	-
C3	High turtleneck shirt	-	-
C4	Upper outer shoulder, Low-collar shirt	Shoulder abduction	Nil
C 5	Outer arm, forearm	Shoulder abduction, elbow flexion	Bicep
C6	Index and thumb	Wrist extension	Supinator
C7	Middle finger centre of palm	Finger and elbow extension	Triceps
C8	Little and ring finger, ulnar border of hand	Wrist/finger flexion	Finger jerk

C6: Make a 6 with your left hand by touching the tip of the thumb & index finger together

Symptoms and signs of a C6 root lesion include

- Paraesthesias in the thumb or lateral distal forearm
- Weakness of brachioradialis, biceps, or triceps and
- Diminished biceps and brachioradialis reflexes in conjunction with an increased triceps reflex.

Winging of the scapula is caused by paralysis of the long thoracic nerve to serratus anterior (C5, 6, 7).

Spinal lesion at the level of C8:

 Weakness of finger flexion + Loss of sensation over the medial aspect of the arm; forearm and hand (Lateral aspect of arm is C5)

Erb-Duchenne palsy ('waiter's tip')

- due to damage of the upper trunk of the brachial plexus (C5,C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

Weakness of shoulder abduction

- May be due to C5 or an axillary nerve lesion:
 - ⇒ C5 lesion
 - weakness of biceps (C5, C6)
 - loss of the sensation of the lateral aspect of the upper arm
 - **⇒** Axillary nerve lesion
 - spinal root : C5/C6

- motor function: innervate teres minor and deltoid muscles
- sensory function: give rise to superior lateral cutaneous nerve of arm which innervate the skin over the lower deltoid (regimental badge area)
- loss of sensation of the regimental badge area
- Absence of sensory loss indicates a lesion at the anterior horn cell.

Thoracic roots

Root	Dermatome	Myotome	Reflex
T 4	Nipples		
T 5	Inframammary fold		
T 7	Xiphoid process		
T 10	Umbilicus		

T1 nerve root injury:

damage to both the median and ulnar nerves -> Global muscle wasting of the hand

Lumber roots

Root	Dermatome	Myotome	Reflex
L1	Inguinal ligament	-	-
L2	Upper anterior and medial thigh	Psoas hip abductor	-
L3	Mid anterior and medial thigh	Psoas quadriceps	Patella (L3,L4)
L4	Knee caps, medial aspect of leg, lower lateral thigh	Tibialis anterior, extensor halluces	Patella (L3,L4)
L5	Big toe, dorsum of foot (except lateral aspect), lateral aspect of leg	Extensor halluces, peroneal, gluteus medias, dorsiflexors, hamstrings	L5 has no reflex. Therefore, an acute lumber disc prolapse resulting in L5 radiculopathy is commonly misdiagnosed as malingering.

L1: Inguinal ligament (L for ligament, 1 for 1nguinal)

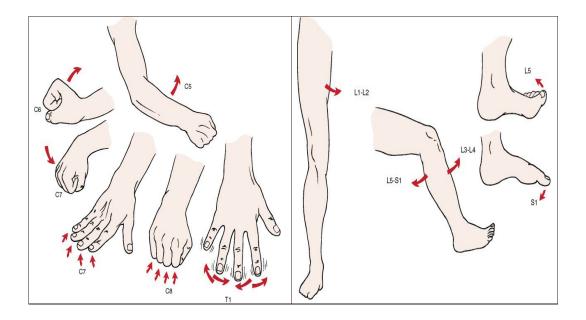
The L4 dermatome is located at the knee caps

L5 = Largest of the 5 toes

L5 lesion features: loss of foot/big toe dorsiflexion + sensory loss dorsum of foot

Sacral roots

Root	Dermatome	Myotome	Reflex
S1	Lateral foot, small toe . sole of the foot.	Peroneal planter flexor	Ankle (S1, S2)
	Posterior, lateral thigh and calf	liexol	
S2	Popliteal fossa	-	Ankle (S1, S2)
S3 -5	Medial buttock and perianal skin in a concentric manner with S3 most lateral and S5 closest to the anus	Bladder, rectum	S2-4 reflex is part of the ano- cutaneous reflex or anal wink.



Deep tendon reflexes: which test for which nerve root?

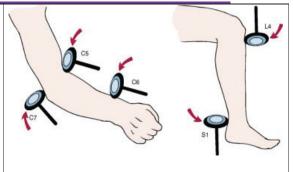
C5 – Biceps

C6 - Biceps, Brachioradialis

C7 – Triceps

L4 – Patellar (knee jerk) (femoral nerve mediated)

S1 – Achilles (ankle jerk) (tibial nerve mediated)



 An inverted supinator jerk, where the biceps jerk is absent but generates a supinator jerk with reflex flexion of the fingers, is indicative of cervical myelopathy with <u>C5/6</u> nerve root damage.

MRCPUK-part-1-September 2019 exam: H/O neck & arm pain like 'electric shocks', worse on turning head + decreased sensation on the dorsal aspect of the thumb and index finger. What is the most likely underlying diagnosis?

→ C6 radiculopathy

MRCPUK-part-1-septemer-2017: Which nerve (and its nerve root) are you tested in triceps reflex?

→ Radial nerve C7

Which spinal dermatome is responsible for the <u>initial</u> vague periumbilical discomfort in appendicitis?

mrcpuk.org SCE sample question: H/O pain affecting buttock region and the lateral border and sole of his foot, in association with paraesthesiae of the sole on walking. What is the correct nomenclature for the nerve root from which these symptoms have arisen?

→ S1 (The S1 nerve root is mapped to the sole of the foot)

Upper limb anatomy

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes
Musculocutaneous nerve (C5-C7)	Elbow flexion (supplies biceps brachii) and supination	Lateral part of the forearm	Isolated injury rare - usually injured as part of brachial plexus injury
Axillary nerve (C5, C6)	Shoulder abduction (deltoid muscle)	Inferior region of the deltoid muscle	Humeral neck fracture/dislocation Results in flattened deltoid
Radial nerve (C5-C8)	Extension (forearm, wrist, fingers, thumb)	Small area between the dorsal aspect of the 1st and 2nd metacarpals	Humeral midshaft fracture Palsy results in wrist drop
Median nerve (C6, C8, T1)	LOAF* muscles Features depend on the site of the lesion: • wrist: paralysis of thenar muscles, opponens pollicis • elbow: loss of pronation of forearm and weak wrist flexion	Palmar aspect of lateral 3 and half fingers	Wrist lesion → carpal tunnel syndrome
Ulnar nerve (C8, T1)	Intrinsic hand muscles except LOAF* Wrist flexion	Medial 1and half fingers	Medial epicondyle fracture Damage may result in a 'claw hand'
Long thoracic nerve (C5-C7)	Serratus anterior		Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy Damage results in a winged scapula

*LOAF muscles

- Lateral two lumbricals
- Opponens pollisAbductor pollis brevis
- Flexor pollis brevis

Overview

- arises from the posterior cord of the brachial plexus (C5-8)
- It is susceptible to compression or traumatic damage as it winds around the humerus (including 'Saturday night palsy', a pressure palsy sustained while sleeping in an awkward position under the influence of alcohol).
- may also be compressed in the axilla (eg from using a crutch).

Regions innervated

Motor (main nerve)	TricepsAnconeusBrachioradialisExtensor carpi radialis
Motor (posterior interosseous branch)	 Supinator Extensor carpi ulnaris Extensor digitorum Extensor indicis Extensor digiti minimi Extensor pollicis longus and brevis Abductor pollicis longus
Sensory	 Dorsal aspect of lateral 3 1/2 fingers The commonest site of sensory loss is at the anatomical snuffbox (small area between the dorsal aspect of the 1st and 2nd metacarpals)

Patterns of damage

- wrist drop with hand pronation and thumb adduction
- sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above
- · paralysis of triceps

Features according to site of damage

Site of lesion	Sensory symptoms	Motor symptoms
Axilla	All below	All belowParalysis of triceps m
Mid-arm	All below Numbness, paresthesia, pain along lateral posterior arm	 All below Wrist drop ⇒ weakness of extensors (hand, finger and wrist joint).
Elbow (radial tunnel)	Pain and tenderness following extension or repetitive pronation/supination	Sometimes weakness of extension and supination, secondary to pain (not to missing innervation)
Deep Forearm (posterior interosseous nerve)	• None	 Paralysis of the finger extensors (no true wrist drop)
Superficial forearm and wrist (superficial radial nerve)	Deficits on the radial side of the dorsum of the hand (thumb, index finger, and the radial half of the middle finger)	None

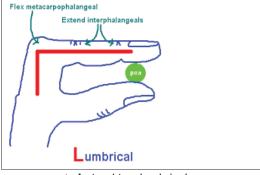
Common questions about radial nerve:

Question	Answer	
Rout?	C5-8	
Typical injury	 Fractured midshaft of humerus/compression of axilla by chair- crutches. 'Saturday night palsy', 	
Motor loss?	extensor muscles (forearm, wrist, fingers, thumb)	
Sensory loss?	dorsal aspect of lateral 3 1/2 fingersanatomical snuffbox	
The commonest site of sensory loss	anatomical snuffbox (small area between the dorsal aspect of the 1st and 2nd metacarpals)	
Sign?	wrist drop	

Median nerve

Overview

- arises from lateral and medial cords of the brachial plexus (C6-8, T1)
- Motor to (LOAF)



When look at hand in this position, can see this makes an "L" shape, since L Lumbrical.

- ⇒ Lateral two lumbricals
- ⇒ Opponens pollicis → rotates and flexes the thumb
- \Rightarrow Abductor pollicis brevis \rightarrow Abduction and opposition of the thumb
- ⇒ Flexor pollicis brevis → Flexes the thumb at the first metacarpophalangeal joint
- the above three form the thenar eminence muscles
- also supplies flexor muscles of the forearm
- Sensory to → palmar aspect of lateral (radial) 3 1/2 fingers

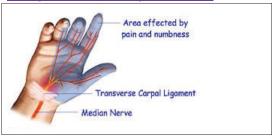
Patterns of damage

- Damage at wrist
 - ⇒ e.g. carpal tunnel syndrome
 - ⇒ paralysis and wasting of thenar eminence muscles
 - ⇒ sensory loss to palmar aspect of lateral (radial) 3 1/2 fingers
- Damage at elbow, as above plus:
 - ⇒ unable to pronate forearm
 - ⇒ weak wrist flexion
 - ⇒ ulnar deviation of wrist
- Anterior interosseous nerve (branch of median nerve)
 - ⇒ leaves just below the elbow
 - ⇒ results in loss of pronation of forearm and weakness of long flexors of thumb and index finger

Common questions about median nerve:

Question	Answer
Rout	C6-8, T1
Typical injury?	Fracture of supracondylar humerus/ Carpal tunnel syndrome
Motor deficit?	Opposition of thumb/Lateral finger flexion (ulnar deviation of wrist)/wrist flexion /(LOAF) muscles
Sensory deficit	Dorsal-palmar lateral 3.5 fingers/thenar eminence
Sign?	Ape hand (loss of Opponens pollicis)/Pope's hand (open digits 1-3 when trying to make fist)

Carpal tunnel syndrome



Overview

- Carpal tunnel syndrome is caused by compression of median nerve in the carpal tunnel.
- More common in females (F:M, up to 8:1).
- Commonly bilateral with dominant hand typically affected first.

Causes

- idiopathic
- pregnancy
- · oedema e.g. heart failure
- lunate fracture
- · rheumatoid arthritis

History

- pain/pins and needles in thumb, index, middle finger
- unusually the symptoms may 'ascend' proximally
- · patient shakes his hand to obtain relief, classically at night

Examination

- weakness of thumb abduction (abductor pollicis brevis)
- wasting of thenar eminence (NOT **hypo**thenar → supplied by ulnar nerve)
- Tinel's sign: tapping causes paraesthesia
- Phalen's sign: flexion of wrist for 60 seconds causes symptoms
- Which area supplied by the median nerve will be spared if the problem is at the carpal tunnel?
 - > the skin over the thenar eminence
 - The palmar cutaneous branch of the median nerve lies superficial to the flexor retinaculum and does not pass through the carpal tunnel. It supplies the skin over the thenar eminence, which is therefore spared in carpal tunnel syndrome.

Electrophysiology

- The most appropriate further investigation → Electromyogram (EMG)/nerve conduction studies
 - ⇒ (EMG)/nerve conduction study is useful for confirming clinical diagnosis prior to actual surgery.
 - ⇒ nerve conduction studies show:
 - decreased conduction velocity in the median nerve.
 - prolongation of the action potential

Treatment

- In patients with mild carpal tunnel syndrome the management should be <u>behavior</u> modification.
- corticosteroid injection
- · wrist splints at night
- surgical decompression (flexor retinaculum division)

Pronator teres syndrome

Definition

 entrapment of the median nerve between the two heads of the pronator teres muscle at the elbow

Features

 The characteristic physical finding is tenderness over the proximal median nerve, which is aggravated by resisted pronation of the forearm.

Diagnosis

- Examination involves excluding carpal tunnel syndrome and pronation of the affected forearm against resistance, which brings on the pain.
 - ⇒ Unlike carpal tunnel syndrome, the median nerve proximal to the wrist may be tender to palpation.

Treatment

 Injection of corticosteroids into the pronator teres muscle may produce relief of symptoms, but a strong response to a steroid injection would be more consistent with carpal tunnel syndrome

Anterior interosseous syndrome

Definition

- Anterior interosseous syndrome or Kiloh-Nevin syndrome is a damage to the anterior interosseous nerve, a motor branch of the median nerve, which arises just below the elbow.
- innervates the long flexor muscles of the thumb (Flexor pollicis longus), index and middle finger (flexor digitorum profundus).

Causes

• neuritis (inflammation of the nerve) in most cases, compression or Trauma

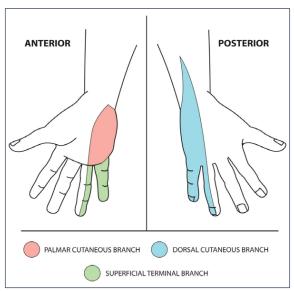
Feature

- Pain in the forearm
- Characteristic weakness of the pincer movement of the thumb and index finger.
- If asked to make the "OK" sign, patients will make a triangle sign instead.
 - ⇒ This 'Pinch-Test' exposes the weakness of the Flexor pollicis longus muscle and the flexor digitorum profundus leading to weakness of the flexion of the distal phalanges of the thumb and index finger.
- Difficulty picking up a small item, such as a coin, from a flat surface

Diagnosis

 Electromyography (EMG) is generally most useful and will reveal abnormalities in the flexor pollicis longus, flexor digitorum profundus I and II and pronator quadratus muscles.

Ulnar nerve



Overview

- Root
 - ⇒ arises from medial cord of brachial plexus (C8, T1)
- Motor innervation
 - ⇒ Third and fourth lumbricals (medial two lumbricals)
 - ⇒ Flex at metacarpal phalangeal (MCP) joint
 - ⇒ Extend at proximal interphalangeal (PIP) joint
 - ⇒ Adductor pollicis: adducts the thumb
 - ⇒ Abductor digiti minimi: abducts the little finger
 - ⇒ Flexor carpi ulnaris: helps flex the wrist
 - ⇒ Dorsal and palmar interossei: finger abduction and adduction respectively
 - ⇒ Flexor digiti minimi brevis: flexes the MCP joint
- Sensory innervation
 - ⇒ medial 1 1/2 fingers (palmar and dorsal aspects)

Causes

- The ulnar nerve is most commonly compressed at or near the cubital tunnel of the elbow and Guyon canal of the wrist.
 - ⇒ Cubital tunnel syndrome (ulnar nerve compression at the elbow)
 - Leaning on the elbow or prolonged elbow flexion during occupational activities (e.g., leaning on a desk), athletic activities, or surgical procedures (e.g., during general anesthesia)
 - Blunt trauma
 - Masses (e.g., tumors, hematomas)
 - Metabolic abnormalities (e.g., diabetes)
 - Guyon canal syndrome (ulnar nerve compression <u>at the wrist</u> in Guyon's canal)
 - Often associated with cycling, likely caused by direct pressure from the handlebars

- Blunt trauma (e.g., hook of hamate fracture)
- Masses (especially ganglion cysts)
- · The most common ulnar neuropathies are
 - - the commonest site for entrapment of ulnar nerve
 - caused by ulnar nerve compression at the elbow
 - may be due to chronic pressure, leaning on the elbows, and direct trauma.
 - ⇒ ulnar tunnel syndrome
 - caused by ulnar nerve compression at the wrist in Guyon's canal

Risk factors

• Ulnar neuropathy is a common complication with ill patients in hospital.

Features

- Wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals)
- Claw hand (where the little and ring fingers curl into the palm).
 - ⇒ hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- Weak pinch (Froment sign)
 - ⇒ little finger in persistent abduction due to weak third palmar interosseous muscle
- Radial deviation of wrist
- Wartenberg sign: little finger in persistent abduction due to weak third palmar interosseous muscle
- Froment sign: The thumb flexes at the interphalangeal joint while pinching a piece of paper to compensate for a weak adductor pollicis muscle.
- Sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)

Proximal and distal lesions of the ulnar nerve lead to claw hand deformity.

Diagnosis

Nerve conduction studies will confirm the site of the lesion.

Common questions about ulnar nerve

Question	Answer
Rout ?	C8-T1
Typical injury?	Fracture of epicondyle of humerus
Motor deficit?	Medial finger flexion/wrist flexion
Sensory deficit?	Medial 1.5 fingers/hypothenar eminence
Sign?	Radial deviation of wrist upon flexion/claw hand

MRCPUK-part-1-sep 2017: H/O dropping things on a frequent basis and muscle wasting at the back of the right hand. On examination, you note wasting of the dorsal interossei. What is the nerve supply of the dorsal interossei?

→ C8/T1

Rotator cuff muscles

Muscle	Notes
Supraspinatus	aBDucts arm before deltoid Most commonly injured
Infraspinatus	Rotates arm laterally
teres minor	aDDucts & rotates arm laterally
Subscapularis	aDDuct & rotates arm medially

Klumpke's palsy

Definition

- Injury to the lower trunk of the brachial plexus (C8–T1)
- This root eventually supplies the **median and ulnar nerves**.
- The ulnar nerve supplies all of the intrinsic hand muscles except for those of the thenar
 eminence and the <u>first and second lumbricals which are innervated by the median</u>
 nerve.

Causes

- Hyperabduction of the arm
 - ⇒ Trauma (e.g., breaking a fall by grabbing a branch)
 - ⇒ Birth injury: excessive upward traction on the arm during delivery
- **Compression** of the lower trunk of brachial plexus (subacute to chronic onset)
 - ⇒ Pancoast tumor
 - □ Cervical rib

Features

- Weakness of intrinsic hand muscles (thenar, hypothenar, lumbricals, interossei) → total claw hand (persistent flexion of the interphalangeal joints and extension of the metacarpophalangeal joints in the hand)
- Preganglionic Horner syndrome if injury occurs proximal to the white ramus communicans
- Decreased peripheral pulses if subclavian vessels are compressed by a Pancoast tumor or cervical rib.
- Sensory loss in the C8 and T1 dermatomes (little finger and medial surface of the forearm and arm)

Treatment

- Splinting the hand to correct the claw hand
- Physiotherapy
- Surgery for severe nerve damage

Stretch injury of the arm

Sudden upward movement of the abducted arm (fall that has been stopped by grasping a
fixed object with one hand) → causes features of an ulnar nerve palsy which is supplied
by the lower brachial plexus roots C8 and T1 (Klumpke's paralysis)

8

Commonly tested nerves of the lower limbs

The information below contains selected facts which commonly appear in examinations:

Nerve	Motor	Sensory	Typical mechanism of injury & notes	
Femoral nerve	Knee extension, thigh flexion	Anterior and medial aspect of the thigh and lower leg	Hip and pelvic fracturesStab/gunshot wounds	
Obturator nerve	Thigh adduction	Medial thigh	Anterior hip dislocation	
Lateral cutaneous nerve of the thigh	None	Lateral and posterior surfaces of the thigh	Compression of the nerve near the ASIS \rightarrow meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve	
Tibial nerve	Foot plantarflexion and inversion	Sole of foot	 Not commonly injured as deep and well protected. Popliteal lacerations, posterior knee dislocation 	
Common peroneal nerve	Foot dorsiflexion and eversion Extensor hallucis longus	Dorsum of the foot and the lower lateral part of the leg	 Injury often occurs at the neck of the fibula Tightly applied lower limb plaster cast Injury causes foot drop 	
Superior gluteal nerve	Hip abduction	None	 Misplaced intramuscular injection Hip surgery Pelvic fracture Posterior hip dislocation Injury results in a positive Trendelenburg sign 	
Inferior gluteal nerve	Hip extension and lateral rotation	None	 Generally injured in association with the sciatic nerve Injury results in difficulty rising from seated position. Can't jump, can't climb stairs 	

Sciatic nerve palsy

Nerve root

- L4-S3
- Sciatic nerve splits into tibial nerve and common peroneal nerve

Causes

- Total hip arthroplasty
 - ⇒ known complication of a <u>total hip replacement</u> (femoral nerve palsy can occur but is much less common).
- Herniated lumbar disc
- Posterior hip dislocation
- latrogenic (misplaced intragluteal injection)

Feature

- Motor
 - ⇒ Impaired knee flexion and hip adduction
 - ➡ Global weakness of the ankle due to the involvement of both of its branches: tibial nerve (plantaflexion and inversion) and common peroneal nerve (dorsiflexion and eversion).
 - **⇒** Absent ankle jerk is due to tibial nerve involvement.

Sensory

- ⇒ Sensory loss is variable but most commonly occurs around the dorsum of the foot and lateral aspect of the leg
- ⇒ Tibial nerve injury → Sensory loss over sole of the foot
- ⇒ The skin over the medial malleolus and medial border of the foot is innervated by the saphenous nerve and is therefore spared.

Injuries of sciatic nerve branches

	Common peroneal nerve injury	Tibial nerve injury
Nerve root	L4-S2	L4-S3
Common causes	 Fracture of the fibular head Compression: tight casts, sitting cross-legged, lithotomy position during surgery 	 Trauma of the knee or leg (e.g., tibial fracture) Baker cyst (causes proximal lesion) Tarsal tunnel syndrome (causes distal lesion)
Motor deficit	 Superficial peroneal nerve: paralysis of peroneus longus and peroneus brevis → impaired eversion of the foot Deep peroneal nerve: paralysis of foot and toe extensors (dorsiflexors) (e.g., tibialis anterior), leading to: Foot drop Steppage gait 	 Paralysis of biceps femoris (long head) Paralysis of foot flexors (e.g., triceps surae) → inability to stand on or curl toes and to invert foot Proximal lesions: eversion of the foot at rest
Sensory deficit	 Superficial peroneal nerve: lateral surface of the lower leg, dorsum of the feet and toes, except for the space between the first and second toe Deep peroneal nerve: area between the first and second toes (flip-flop zone) 	Sensory loss over sole of the foot

Common peroneal nerve lesion

The commonest cause of acute foot drop after prolonged bed rest is entrapment common peroneal neuropathy at the neck of fibula.

Overview

- The sciatic nerve divides into the tibial and common peroneal nerves in the popliteal fossa.
- Nerve root → L4–S2
- Common peroneal nerve divides into a superficial and a deep branch
 - ⇒ Deep peroneal nerve supplies muscles, which dorsiflex the foot and toes:
 - tibialis anterior
 - extensor hallucis longus
 - extensor digitorum longus
 - ⇒ Superficial nerve supplies the muscles, which evert the foot
 - peroneus longus and brevis

• Injury often occurs at the neck of the fibula.

Causes

- · Fracture of the fibular head
- Compression: tight casts, sitting cross-legged, lithotomy position during surgery

Features

- Foot drop (the most characteristic feature)
 - ⇒ Superficial peroneal nerve: paralysis of peroneus longus and peroneus brevis → impaired eversion of the foot
 - ⇒ Deep peroneal nerve: paralysis of foot and toe extensors (dorsiflexors) (e.g., tibialis anterior), leading to: Foot drop and Steppage gait
- Sensory loss over the dorsum of the foot and the lower lateral part of the leg with sparing of the fifth toe.
 - ⇒ Superficial peroneal nerve: lateral surface of the lower leg, dorsum of the feet and toes, except for the space between the first and second toe
 - ⇒ Deep peroneal nerve: area between the first and second toes (flip-flop zone)

Foot-drop

- Weakness of eversion + dorsiflexion + inversion → L4 5 radiculopathy
- Weakness of eversion + dorsiflexion → common peroneal nerve palsy (ankle inversion is spared with common peroneal nerve palsy)

Differences between tibial nerve and peroneal nerve injuries:

- Tibial → impaired foot Inversion and Plantarflexion
- Peroneal → impaired foot Eversion and Dorsiflexion

Femoral nerve palsy

Nerve root

L2-L4

Causes

- Compression: Prolonged pressure on the nerve:
 - ⇒ Psoas haematoma (due to anticoagulant therapy or haemophilia), Psoas abscess
 - ⇒ Tumours eg: Synovial cyst, Sarcoma
 - ⇒ Aortic or iliac aneurysms
- Trauma: Direct injury to the nerve
 - ⇒ Hip or pelvic fractures
 - ⇒ latrogenic: eg: Hip arthroplasty, pelvic surgery, femoral line placement, coronary angiography).
- **Diabetic amyotrophy** (proximal neuropathy, in diabetic patients, causes burning pain in the hip and thigh and wasting of thigh muscles)

Feature

- Motor
 - ⇒ Paralysis of iliopsoas, pectineus, rectus femoris, and sartorius muscles → impaired hip flexion
 - ⇒ Paralysis of quadriceps femoris muscle →
 - Impaired knee extension: instability of the knee (often described as 'buckling') on climbing stairs.
 - Decreased patellar tendon reflex (absent knee jerk)
- Sensory
 - ⇒ Decreased sensation in **anterior thigh** (meralgia paraesthetica) and **medial distal leg** (saphenous nerve)

Hip weakness:

- Weakness of hip Abduction (Gluteus medius) → superior gluteal nerve palsy
- Weakness of hip adduction (Adductor magnus and minimus) → Obturator nerve palsy
- Weakness of hip flexion (iliopsoas muscle) → Femoral nerve palsy
- Weakness of hip extension (Gluteus maximus) → inferior gluteal nerve

Obturator nerve injury

- Root: L2–L4
- Common causes: Pelvic surgery, pelvic ring fractures
- Motor deficits: Paralysis of hip adductors (adductor longus, adductor brevis, adductor magnus, obturator externus, gracilis, pectineus)
- Sensory deficits: Howship-Romberg sign: pain and paresthesia over the inner aspect
 of the thigh.

Meralgia paraesthetica

Burning thigh pain - ? meralgia paraesthetica - lateral cutaneous nerve of thigh compression

Nerve root

L2-L4

Pathology

compression of lateral cutaneous nerve of thigh

Causes of compression

- Most likely causes→ entrapment at the lateral inquinal ligament:
 - ⇒ Increased intra-abdominal pressure (e.g., pregnancy, obesity, ascites)
 - ⇒ External compression (e.g., tight belts, pants, or compression dressings)
 - ⇒ Local compression (e.g., tumors, hematomas)
- Less likely causes → trauma, ischaemia, or a retroperitoneal lesion.

Features

- · typically burning sensation over antero-lateral aspect of thigh
- pure sensory loss
- · numbness when tapping on the inguinal ligament

Treatment

Can be improved by wearing looser clothing and/or losing weight

Healthy patient came with burning thigh pain. What is the next step in management?

→ Advice the patient to wear loose pant

MRCPUK-part-1- May 2006 exam: A patient presents with a burning sensation over anterolateral aspect of thigh. Which nerve is most likely to be affected?

→ Lateral cutaneous nerve of thigh

Saphenous nerve injury

Overview

- Saphenous nerve is a terminal cutaneous branch of the femoral nerve.
- It is supplies the skin over the anteromedial side of the knee, leg and medial malleolus.
- It is strictly a sensory nerve; it has no motor component.
- It is commonly blocked to complement anesthesia of the lower leg.

Causes

- Saphenous vein harvest for coronary artery bypass grafting (CABG) (most common).
- Femoral artery catheterization for angiography.
- Trochanter placement during knee arthroscopy.
- Long saphenous vein stripping for varicose veins.

Features

· Loss of sensation over the medial aspect of the lower leg.

Tarsal tunnel syndrome

Tarsal tunnel syndrome

entrapment of the posterior tibial nerve as it travels through the tarsal tunnel, this tunnel is found along the inner leg behind the medial malleolus \rightarrow painful foot

Overview

- also, known as posterior tibial neuralgia
- It is analogous to carpal tunnel syndrome of the wrist.

Definition

 peripheral neuropathy caused by compression of the tibial nerve by the flexor retinaculum of the foot at the medial ankle

Causes

- Trauma (most common): fracture or sprain of the ankle (talus, calcaneus, medial malleolus)
- Rheumatoid arthritis

Features

- Symptoms develop in areas innervated by the tibial nerve (distal to the medial malleolus):
 - ⇒ Neuropathic pain and paresthesia in the heel, sole of the foot, and first three toes
 - **⇒ Weakness and atrophy of intrinsic foot muscles** (severe cases)
- Symptoms worsen with walking, prolonged standing, and at night

Diagnosis

- •
- Usually a clinical diagnosis
- Positive **Tinel sign**: radiating paresthesia triggered by tapping the flexor retinaculum posterior to the medial malleolus
- Pain upon foot dorsiflexion with eversion
- Diminished sensation on the plantar area of the foot
- Nerve conduction studies: slow conduction velocity in the medial and lateral plantar nerves

Treatment

- Initially conservative (Rest, NSAIDs, physiotherapy, use of orthotic shoes)
- Local injection of steroids into the tarsal canal (if no improvement)
- Surgical decompression

Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Cardiology

Updated 2022

Coronary arteries: anatomy and clinical correlation

- Right coronary artery (RCA)
 - ⇒ supplies:
 - AV node, so heart block following inferior MI is common. However, heart block following anterior MI is a grave prognostic marker as this indicates a large anterior wall infarct. RCA supplies SA node in 60%, AV node in 90%
 - Right ventricle, hence, problems relating to a right ventricular infarct are commonly associated with an inferior MI.
 - Inferior myocardium and occlusion causes ST elevation in II, III and aVF.
 - ⇒ **Posterior descending artery** a <u>branch of the right coronary artery in 85%</u> of people (a branch of the circumflex in the remaining population).
 - supplies the posterior left ventricular myocardium
 - occlusion causes <u>posterior MI</u> (ST depression in V1-V4 with a dominant R wave in V1).
 - The concept of coronary dominance refers to which coronary artery supplies the posterior descending coronary artery (PDA).
 - ❖ 85% of patients having a dominant right coronary artery
 - 15% of patients having a dominant left circumflex.
- Left main stem left coronary artery (LCA)
 - ⇒ **Supplies** most of the left ventricle.
 - ⇒ Complete left main stem occlusion is invariably fatal. It would produce extensive ST elevation across all the chest leads, I and aVL and possibly aVR, too.
 - ⇒ LCA branches into → Left Anterior Descending (LAD) + Left Circumflex artery (LCX)
 - Left Anterior Descending (LAD) artery
 - supplies : anterior and septum
 - ❖ Occlusion →ST segment elevation in leads V1-V4
 - Right bundle branch block in acute anterior myocardial infarction suggests obstruction prior to the first septal branch of the left anterior descending coronary artery
 - Left Circumflex artery (LCX)
 - Supplies : lateral
 - Occlusion produces ST elevation in V5, V6, I and aVL.

ECG localization of STEMI

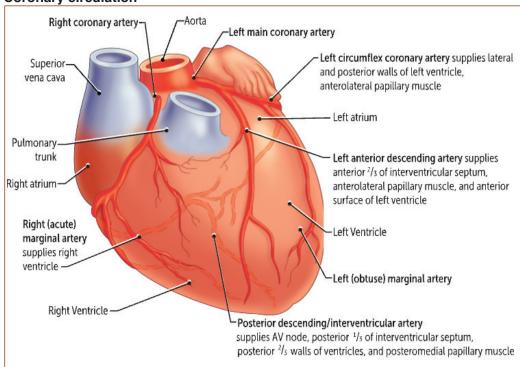
ECG leads with ST elevation	Infarction location	
V1 – V2	Anteroseptal (LAD)	
V3- V4	Antero-apical (distal LAD)	
V5- V6	Antero-lateral (LAD or LCX)	
I, aVL	Lateral (LCX)	
II, III, aVF	Inferior (RCA)	
V7 – V9, ST depression V1- V3 with tall R waves	Posterior (PDA)	

ST-segment elevations or Q waves in leads II, III, and aVF on ECG signify a likely inferior MI, supplied by the right coronary artery.

Coronary arterial dominance

- Right-dominant (~ 85% of the population): posterior descending artery (PDA) supplied by the RCA
- Left-dominant (~ 8% of the population): PDA supplied by the left circumflex artery (LCX)
- Codominant (balanced; ~ 7% of people): PDA supplied by both RCA and LCX

Coronary circulation



The left atrium is the posteriormost part of the heart, located directly in front of the esophagus. It can be visualized using TEE. The right ventricle is the anteriormost part of the heart and is at greatest risk of injury following chest trauma.

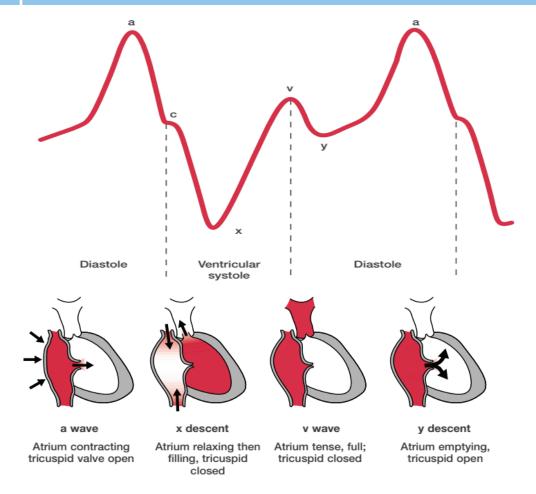
Jugular venous pulse (JVP)

JVP: C wave - closure of the tricuspid valve

JVP: x descent = fall in atrial pressure during ventricular systole

JVP: y descent = opening of tricuspid valve

JVP: giant v waves in tricuspid regurgitation



Clinical importance of JVP

- · providing information on right atrial pressure,
- may provide clues to underlying valvular disease.
- A non-pulsatile JVP is seen in superior vena caval obstruction.
- Kussmaul's sign describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis.

JVP waves and abnormalities			
Wave	Description	Abnormalities	
a wave	 The first peak caused by atrial contraction 	Absent in atrial fibrillation	
c wave	The second peak caused by tricuspid valve closure, contraction of the right ventricle, and bulging of the tricuspid valve into the right atrium	cv wave : severe tricuspid valve regurgitation	
x descent	A drop in JVP caused by atrial relaxation during ventricular systole	Absent in: Tricuspid valve regurgitation Right heart failure	
v wave	The third peak caused by venous refilling of the right atrium against the closed tricuspid valve	 Prominent in: Tricuspid valve regurgitation Right heart failure 	
y descent	 A drop in JVP caused by decreased right atrial pressure as blood flows into the right ventricle after opening of the tricuspid valve 	 Prominent in: Tricuspid valve regurgitation Constrictive pericarditis Absent in: Cardiac tamponade Tricuspid valve stenosis 	

Cannon 'a' waves

- Caused by atrial contractions against a closed tricuspid valve
- Causes
 - ⇒ Regular cannon waves
 - ventricular tachycardia (with 1:1 ventricular-atrial conduction)
 - atrio-ventricular nodal re-entry tachycardia (AVNRT)
 - ⇒ Irregular cannon waves
 - complete heart block

A left sided internal jugular central venous catheter has been inserted and you are reviewing the chest radiograph to check the position of the tip of the catheter. What is the safest position to leave the catheter tip?

○ In the lower superior vena cava

Central venous access of the Subclavian Vein

Anatomy

- Each subclavian vein is a continuation of the axillary vein and runs from the outer border of the first rib.
- The subclavian and internal jugular vein unite to form the brachiocephalic vein,
 subsequently the left and right brachiocephalic veins unite to form the superior vena cava.

Procedure

- Left-sided subclavian access is associated with lower rates of catheter malposition and vessel trauma. It is preferred when immediate cardiac access is needed (eg, temporary transvenous pacer and pulmonary artery catheter insertion) since the guidewire and catheter are more easily directed into the superior vena cava and right heart.
- The optimal point of needle insertion:
 - ⇒ 1 cm inferior to the junction of the middle and medial third of the clavicle.

Advantages

- the cleanest site for central venous access (lower potential for infection).
- It also the most tolerated by patients.
- consistent landmarks (lower potential for arterial injury compared with other sites of access).

Complications

- Arrhythmias (e.g. premature atrial and ventricular contractions) caused by contact of the guidewire to the right atrium.
- Venous air embolism, pneumothorax, and pneumomediastinum are other common complications of central line placement.
- subclinical pneumothorax even in the hands of experienced clinicians.

Central venous access

- Ultrasound guidance improves initial cannulation success.
- Obtain a postprocedural chest x-ray to confirm catheter position and exclude pneumothorax in jugular and subclavian catheters. Femoral catheters do not require radiographic confirmation and can be used immediately following insertion.
- The internal jugular vein are a commonly used site for central venous access. The
 distal tip of jugular catheters should lie in the lower superior vena cava. Carotid
 artery puncture is a well-recognized complication.
- Femoral site cannulation is often recommended as a secondary site due to higher rates of delayed complications.

Subclavian steal syndrome

Brainstem features (vertigo, diplopia, dysarthria, and drop attacks) with disparity in BP > 15 mm Hg and pain precipitated by exercise → Subclavian steal syndrome

Pathophysiology

- Stenosis of the subclavian artery proximal to the origin of the vertebral artery →
 hypoperfusion distal to the stenosis → reversal of blood flow in ipsilateral vertebral artery →
 compensation through collateral arteries → reduced blood flow in the basilar artery →
 reduced cerebral perfusion upon exertion involving the affected arm
- characterized by <u>retrograde flow</u> into the vertebral or internal thoracic arteries, <u>due</u> to <u>stenosis</u> and/ or <u>occlusion</u> of the <u>subclavian</u> artery.

What is the most likely mechanism that maintains blood flow to the affected extremity?

Blood from the contralateral vertebral artery is shunted away from the basilar artery
(away from the brainstem) and retrograde into the ipsilateral vertebral artery to supply
the affected arm.

Causes

- Atherosclerosis
- Takayasu's arteritis

Symptoms

The most common symptoms are those related to <u>upper limb ischemia</u> (arm pain and numbness, especially during exertion and exercise with the arm above the head, such as painting a wall.)

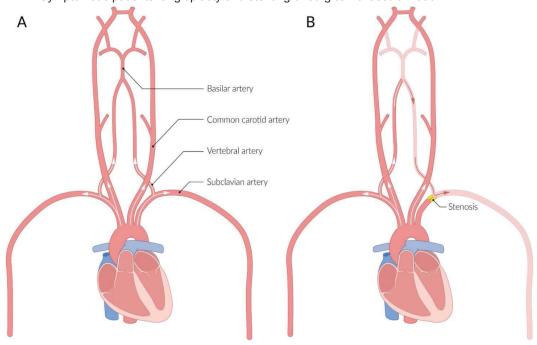
- brainstem features due to vertebrobasilar insufficiency such as: Vertigo, Diplopia, Dysarthria, and Drop attacks.
- · blood pressure is different between the upper limbs by at least 15 mmHg.

Diagnosis

- Duplex ultrasound is the best initial radiological test ⇒ shows reversal of blood flow (retrograde flow in the ipsilateral vertebral artery)
- Angiography of the subclavian vessels (MRA) is the most accurate test.

Management

- Most patients require no intervention
- Symptomatic patients: angioplasty and stenting or surgical revascularization



Pathophysiology of subclavian steal syndrome

Under normal conditions, the subclavian artery distributes blood equally to the arteries in the brain and arms (A). If there is stenosis of the subclavian artery proximal to the origin of the vertebral artery, this leads to hypoperfusion of the upper extremities on the affected side (B). This is compensated by a contralateral circulation, in which there is increased blood flow from the unaffected side to the affected side via the vertebral arteries. As a result, there is hypoperfusion of the vertebrobasilar territory and corresponding central nervous system symptoms.

Atrial natriuretic peptide (ANP)

Secretion

- Released from atrial myocytes (right > left) in response to blood volume and atrial pressure.
- Acts via cGMP

ANP secretion pathway and actions

- ↑ Volume → ↑ atrial stretch receptors stimulation → release of ANP from atrial cardiomyocytes which results in:
 - ⇒ ↑ Excretion of NaCl and water by the kidneys (via afferent arterioles dilations and efferent arterioles constriction)
 - ⇒ ↓ Na+ reabsorption at the renal collecting tubule (via ↑ cGMP)
 - ⇒ Inhibition of renin
 - ⇒ Vasodilation of veins and arteries (↓ preload and ↓ afterload)
- ↓ Volume → ↓ atrial stretch receptors stimulation → ↓ Release of ANP → ↓ excretion of NaCl and water by the kidneys

How is the "aldosterone escape" mechanism mediated by atrial natriuretic peptide (ANP)?

 ANP causes cGMP-mediated dilation of the afferent arteriole and constriction of the efferent arteriole, promoting diuresis and counteracting the effects of aldosterone

B-type (Brain) Natriuretic Peptide (BNP)

BNP - actions:

- vasodilator
- diuretic and natriuretic
- suppresses both sympathetic tone and the renin-angiotensinaldosterone system

Definition

 B-type natriuretic peptide (BNP) is a hormone produced mainly by the left ventricular myocardium in response to strain (myocyte stretch).

Mechanism of action

- Similar physiologic action to ANP with longer half-life.
- ↑ intracellular smooth muscle cGMP → arterial and venous smooth muscle vasodilatation → ↓ pre-load → ↓BP
- ↓ sodium reabsorption, leading to natriuresis and diuresis.
- suppresses both sympathetic tone and the renin-angiotensin-aldosterone system

Causes of raised BNP levels

- · heart failure is the most obvious cause
- · age over 70 years,
- ventricular hypertrophy, ischaemia, tachycardia, hypoxaemia [including pulmonary embolism], chronic obstructive pulmonary disease,
- renal dysfunction [eGFR less than 60 ml/minute/1.73 m²]
- sepsis,
- diabetes
- cirrhosis of the liver
- BNP synthesis is increased by thyroid hormones as well as glucocorticoids, endothelin-1, angiotensin-II, and tachycardia, independent of the haemodynamic effects of these factors.

Factors which reduce BNP levels

- Obesity
- · African or African-Caribbean family origin
- treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta- blockers, angiotensin II receptor blockers (ARBs) or mineralocorticoid receptor antagonists (MRAs)

Clinical uses of BNP

• Diagnosing patients with acute dyspnoea (very good negative predictive value for heart failure). (NICE guidelines - 2018).

NT-proBNP level	Note
> 2,000 ng/litre	Refer urgently to specialist and echocardiography within
	2 weeks.
Between 400 and	Refer to specialist and echocardiography within 6 weeks.
2,000 ng/litre	
< 400 ng/litre	makes a diagnosis of heart failure less likely

- Prognosis in patients with chronic heart failure: very high levels of NT-proBNP carry a poor prognosis
- Guiding treatment in patients with chronic heart failure: effective treatment lowers BNP levels

Brain natriuretic peptide (BNP)

- BNP a hormone secreted from ventricular myocytes in response to ventricular volume overload, as seen in congestive heart failure.
- BNP acts on the renal collecting duct to decrease sodium reabsorption and increases glomerular filtration rate, leading to urinary sodium loss.
- BNP has a good negative predictive value, so a patient with a normal BNP likely does not have heart failure.

Cardiovascular physiology

- The basic muscle unit of the myocardium

 ⇒ Sarcomere
- The normal resting cell membrane potential of a cardiac myocyte ⇒ 90 Mv
- Left ventricular ejection fraction (LV EF) = (Stroke volume/end diastolic volume) * 100%
- Cardiac output (CO) measure how much blood ejected by the heart in one minute. CO = Stroke volume (SV) x Heart rate (HR)
- Stroke Volume (SV) volume of blood ejected per heart beat = CO/HR = End-Diastolic Volume (EDV) End-Systolic Volume (ESV)
- Stroke volume is decreased by hypovolaemia
- normal ejection fraction is more than 55% of the blood volume.
- In systolic dysfunction, EF is low. In diastolic dysfunction, EF is normal (called HF with preserved LV EF) e.g. hypertrophic heart failure
- Pulse pressure = Systolic Pressure Diastolic Pressure
 - ⇒ Factors which increase pulse pressure
 - less compliant aorta (this tends to occur with advancing age)
 - increased stroke volume
 - ⇒ Factors which reduced pulse pressure
 - Reduced stroke volume.
 - high aortic compliance,

- reduced venous return, and
- reduced peripheral resistance

Sinoatrial node

- ⇒ has the **fastest firing rate** of all potential pacemakers in the heart.
- ⇒ Sinoatrial node impulses must occur at a rate <u>slower</u> than 200 impulses per minute to be considered in normal sinus rhythm.

• Endothelin

- preferentially constricts renal afferent arterioles.
 - Efferent arteriole vasoconstriction is mediated by angiotensin-II, to defend GFR in states of generalised vasoconstriction and reduced blood flow.
 - efferent arteriole vasodilation will occur when angiotensin-II levels fall.
- ⇒ Stimulates the renin-angiotensin-aldosterone system
- ⇒ Leads to release of atrial natriuretic peptide
- ⇒ Inhibits the action of vasopressin
- ⇒ Two types of endothelin receptor have been characterised, A and B.
 - Binding of endothelin to the A receptor induces vasoconstriction,
 - binding to the B receptor leads to nitric oxide release and hence vasodilatation.

Coronary circulation physiology

- The three most potent factors for vasodilation of the coronaries are:
 - 1. Increased adenosine
 - 2. Increased nitric oxide
 - 3. Opening of ATP-sensitive potassium (KATP) channels by low ATP concentrations, which hyperpolarizes the vascular smooth muscle

Physiological changes during pregnancy

- Heart rate: increases by 10-20 bpm
- Cardiac output and blood volume increase from the second month up to the thirtieth week to 30 - 50% above the normal levels.
- The increase in cardiac output is mediated via increase in both <u>stroke volume</u> and to a lesser extent <u>heart rate</u>, along with a dramatic fall in total <u>peripheral vascular</u> resistance.
- Venous pressure: remain the same due to a 25% reduction in systemic and pulmonary vascular resistance.
- Blood pressure: drop in the first and second trimester due to vasodilatation and then climb to pre-pregnancy levels by the third trimester.
- The increase in blood volume and increased cardiac output lead to <u>all stenosic murmurs</u> <u>becoming more prominent</u> (there is increased flow across the valve, with more turbulence and pressure gradient, leading to a louder sound).
- Increased metabolic workload
- Apex beat is displaced, because of cardiomegaly and a raised diaphragm
- The increased blood flow may produce a <u>pulmonary systolic murmur</u> and a <u>third heart</u> sound.

Which murmur is diminished during pregnancy?

- Aortic regurgitation
 - The fall in diastolic blood pressure during pregnancy leads to a reduction in the murmur of aortic regurgitation.

Physiological changes during exercise

Increases during exercise

- cardiac output → Systemic arterial pressure
- ↑ venous return → ↑stroke volume
- ↑ heart rate

Decreases during exercise

- Venous compliance
- Peripheral vascular resistance
- Diastolic pressure
- Pulmonary vascular resistance
- Dilatation of the blood vessels within the exercising muscles causes a fall in total peripheral resistance, resulting in a decrease in diastolic blood pressure.
- Decrease in venous compliance (dilatation), caused by sympathetic stimulation, helps to maintain ventricular filling during diastole.
- The **pulmonary vessels** undergo <u>passive dilatation</u> as more blood flows into the pulmonary circulation, <u>decreasing pulmonary vascular resistance</u>.

Physiological changes associated with age

- Decrease elasticity and compliance of the aorta → increased resistance to ejection of blood from the left ventricle → increased ventricular afterload.
- Diastolic dysfunction and reduced stroke volume
- ↓↓diastolic pressure (the pressure responsible for subendocardial perfusion) →
 subendocardial ischemia and interstitial fibrosis. (These changes are related to an increase
 in the magnitude of the L-type Ca⁺⁺)
- · Higher systolic arterial pressure and increased impedance to left ventricular ejection
- ↑ systolic + ↓ diastolic → ↑ pulse pressure
- · Increased sino-atrial conduction time
 - Because of the delayed LV relaxation and the stiffer left ventricle, the force of left atrial contraction increases and the contribution of the atrial contraction to LV enddiastolic volume increases
- There is apoptosis of atrial pacemaker cells with a loss of 50%-75% of cells by age 50. The number of atrioventricular nodal cells is preserved and there is fibrosis and cellular loss in the His bundle
- Left ventricular hypertrophy
- Which physiological change associated with age during exercise?
 - **⇒** Reduced tachycardic response

Valsalva manoeuvre

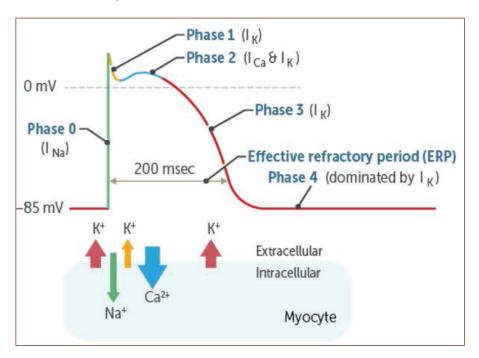
Definition

 The Valsalva manoeuvre describes a forced expiration against a closed glottis. This leads to increased intrathoracic pressure which in turn has a number of effects on the cardiovascular system.

Uses

- to terminate an episode of supraventricular tachycardia
- normalizing middle-ear pressures

Cardiac action potential Cardiac action potential



Phase	Description	Mechanism	
0	Rapid	Rapid sodium influx	
	depolarisation	These channels automatically deactivate after a few ms	
1	Early	Efflux of potassium	
	repolarisation		
2	Plateau	Slow influx of calcium	
3	Final	Efflux of potassium	
	repolarisation		
4	Restoration of	Resting potential is restored by Na ⁺ /K ⁺ ATPase	
	ionic	There is slow entry of Na ⁺ into the cell decreasing the potential	
	concentrations	difference until the threshold potential is reached, triggering a new	
		action potential	

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

Conduction velocity

Site	Speed
Atrial	Spreads along ordinary atrial myocardial fibres at 1 m/sec
conduction	
AV node	0.05 m/sec
conduction	
Ventricular	Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec (this
conduction	allows a rapid and coordinated contraction of the ventricles

Pulses

Patent ductus arteriosus - large volume, bounding, collapsing pulse

Pulsus alternans - seen in left ventricular failure

Pulse	Causes
Pulsus paradoxus (>10 mmHg fall in systolic BP on inspiration)	cardiac tamponade (common)
Pulsus alternans (regular alternation of the force of the arterial pulse between strong and weak)	severe LVF
Bisferiens pulse ('double pulse' - two systolic peaks)	mixed aortic valve disease
Collapsing	aortic regurgitation, patent ductus arteriosus, hyperkinetic (anaemia, thyrotoxic, fever, exercise/pregnancy).
Slow-rising/plateau	aortic stenosis
Jerky pulse	hypertrophic obstructive cardiomyopathy

Pulsus paradoxus

- Definition
 - ⇒ a greater than 10 mmHg fall in systolic BP on inspiration
 - ⇒ → faint or absent pulse in inspiration
- Mechanism
 - ⇒ Inhalation → ↑ venous return → expands right ventricle (RV) → compresses left ventricle (LV) → ↓ blood pressure.
 - ⇒ Inhale = Big RV = Smaller LV = BP drop > 10 mm Hg
- Causes
 - ⇒ cardiac tamponade (common)
 - ⇒ constrictive pericarditis (less commonly than tamponade)
 - ⇒ asthma,
 - ⇒ obstructive sleep apnoea
 - ⇒ croup.

Heart sounds First heart sound (S1): Closure of the mitral and tricuspid valves

Changes in first heart sound (S1)	Causes
Loud S1	 mitral stenosis left to right shunts short PR interval (e.g. WPW type B), (shortened diastole) atrial premature beats hyperdynamic states
Quiet (soft) S1	 mitral regurgitation immobile mitral stenosis if closure of the mitral valve is delayed e.g.: ⇒ LBBB, ⇒ long PR hypodynamic state
Split S1	 right bundle branch block, left bundle branch block, ventricular tachycardia, Ebstein's anomaly
Variable intensity	Atrial fibrillation

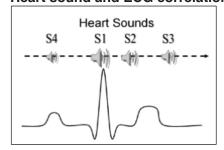
Third heart sound (S3)

Gallop rhythm (S3) is an early sign of LVF

Sound	Origin	Causes	Notes
Third heart sound (S3)	caused by rapid ventricular filling during diastole.	Physiological: ⇒ young individuals (< 40 years of age), athletes, or pregnant women Pathological ⇒ Chronic mitral regurgitation ⇒ Aortic regurgitation ⇔ Heart failure ⇒ Dilated cardiomyopathy Thyrotoxicosis	 Early diastolic sound that is heard immediately after S2 Ventricular gallop: S1 is followed by S2 and S3.
Fourth heart sound (S4)	caused by <u>atrial</u> <u>contraction</u> against a stiff ventricle	Physiological: advanced age Pathological if palpable Ventricular hypertrophy (e.g., hypertension, aortic stenosis, cor pulmonale) Ischemic cardiomyopathy Acute myocardial infarction	 Late diastolic (presystolic) sound heard immediately before S1 P wave on ECG

Gallops that originate from the left side of the heart (the most common) become softer with inspiration, while those that originate from the right side become louder.

Heart sound and ECG correlation



Second heart sound (S2)

Second heart sound (S2)

- · loud: hypertension
- · soft: AS
- · fixed split: ASD
- · reversed split: LBBB

Second heart sound (S2): Closure of the aortic valve (A2) (louder) and pulmonary valve (P2) (softer).

Changes in S2	Causes	
Loud A2	arterial hypertension, coarctation of the aorta	
Loud P2	pulmonary hypertension	
Physiological split (A2 precedes P2).	during inspiration → ↓intrathoracic pressure → ↑venous return to the right side of the heart → prolonged right ventricular systole → delayed closure of P2. Especially pronounced among young individuals	
Wide split	 Mechanism Increased right ventricular afterload → prolonged right ventricular systole Decreased left ventricular preload → shortened left ventricular systole Causes Pulmonary hypertension Pulmonary valve stenosis RBBB Massive pulmonary embolism Severe mitral regurgitation Wolff-Parkinson-White syndrome Constrictive pericarditis 	
Fixed split (Does not change with respiration and tends to be wide, i.e., the split is also audible during expiration)	 Atrial septal defect (ASD)→ RV volume overload → delay in the closure of the pulmonary valve Severe RV failure Right bundle-branch block with heart failure (right bundle-branch block widens the split, and heart failure makes the split fixed). 	
reversed (paradoxical) split S2 (P2 occurs before A2)	Due to delayed A2	
Absent split (No splitting of S2)	Severe aortic stenosis (geriatric)VSD with Eisenmenger syndrome (paediatric)	

Murmurs

Most murmurs of stenosis or regurgitation are exaggerated during squatting and get softer with the Valsalva manoeuvre. The exceptions are HOCM where the opposite occurs (↑ by Valsalva & ↓ by squatting) and mitral valve prolapse where the murmur gets longer.

Relation between murmurs intensity and respiration:

- Murmurs that <u>increase</u> in intensity with <u>inspiration</u> originate from the <u>right side of the</u> <u>heart</u> (tricuspid or pulmonary)
- Murmurs that **increase** in intensity with **expiration** originate from the **left side of the heart** (mitral or aortic).

Mnemonic: RILE (Right Inspiration, Left Expiration)

Murmur	Causes	
Ejection systolic	Aortic stenosis, HOCMPulmonary stenosisASDFallot's	
Holosystolic (pansystolic)	 mitral/tricuspid regurgitation (high-pitched and 'blowing' in character) VSD ('harsh' in character) 	
Late systolic	Mitral valve prolapse Coarctation of aorta	
Early diastolic	 Aortic regurgitation (high-pitched and 'blowing' in character) Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character) 	
Mid-late diastolic	Mitral stenosis Austin-Flint murmur (severe aortic regurgitation, indistinguishable from that of mitral stenosis). It is due to partial closure of the anterior leaflet of the mitral valve by the regurgitant jet.	
Continuous machine- like murmur	patent ductus arteriosus	

Murmurs and the Effects of Maneuvers			
Squatting/ Standing/ Valsalva			
Mitral and aortic stenosis Increases both Decreases both			
Mitral and aortic regurgitation Increases both Decreases both			
Mitral valve prolapse Decrease Increase			
HOCM Decrease Increase		Increase	

More blood increases **all** murmurs except MVP and HOCM.

Standing and Valsalva **decrease** venous return to the heart.

Murmurs in pregnancy

- The intensity of Aortic regurgitation murmur diminishes during pregnancy.
- Diastolic blood pressure is lower due to vasodilatation, and this is responsible for the fading of the aortic regurgitation murmur
- All stenotic murmurs become more prominent

Mitral murmurs are heard best during expiration and while the patients lies on the left side.

All right-sided heart murmurs are intensified during deep inspiration.

Isometric handgrip exercises increase blood pressure and afterload significantly. Therefore, murmurs caused by the backward flow of blood will be accentuated:

- aortic regurgitation,
- mitral valve regurgitation,
- mitral valve prolapse and
- · ventricular septal defect.

<u>Syncope</u>

Definition

 Syncope is a transient <u>loss of consciousness</u> due to transient global cerebral hypoperfusion, characterised by <u>rapid onset</u>, <u>short duration</u>, and <u>spontaneous complete</u> <u>recovery</u>.

Cases

- Syncope can be classified as
 - ⇒ non-cardiovascular causes:
 - neurally-mediated (reflex syncope)
 - vasovagal
 - situational syncope: provoked by straining during micturition (usually while standing) or by coughing or swallowing.
 - secondary to orthostatic hypotension
 - ⇒ cardiovascular causes (such as arrhythmias or ischaemia)
- In older patients, non-cardiovascular causes are twice as common as cardiovascular causes

Evaluation

- The initial evaluation after T-LOC consists of:
 - ⇒ a careful history
 - ⇒ orthostatic BP measurements
 - **⇒** ECG
 - ECG is the most useful test for classifying syncopal episodes into high risk and low risk categories:
 - High risk :history of heart disease or abnormal ECG.
 - Low risk: no underlying diseases and a normal ECG.

- The initial evaluation can define the cause of syncope in 23-50% of patients and should answer three key questions:
 - ⇒ Is it a true syncopal episode or not?
 - ⇒ Has the aetiological diagnosis been determined?
 - ⇒ Are there findings suggestive of a high risk of cardiovascular events or death?
- What you were doing during the episode of blackout?
 - during exercise : exercise-induced syncope occurred (cardiac arrhythmic cause is probable)
 - offer urgent (within 7 days) exercise testing, unless there is a possible contraindication (such as suspected aortic stenosis or hypertrophic cardiomyopathy requiring initial assessment by imaging).
 - Advise the person to refrain from exercise until informed otherwise following further assessment.
 - offer an ambulatory ECG and do not offer a tilt test as a first-line investigation.
 - ❖ TLoC at least several times a week, → offer Holter monitoring (up to 48 hours)
 - ❖ If no further TLoC occurs during the monitoring period, → offer external event recorder that provides continuous recording with the facility for the patient to indicate when a symptomatic event has occurred.
 - **❖ TLoC every 1–2 weeks** → offer an external event recorder.
 - ❖ If the person experiences further TLoC outside the period of external event recording, → offer an implantable event recorder.
 - ❖ TLoC infrequently (less than once every 2 weeks) → offer an implantable event recorder. A Holter monitor should not usually be offered unless there is evidence of a conduction abnormality on the 12lead ECG.
 - ⇒ **shortly after stopping exercise** (vasovagal cause is more likely).
- Unexplained syncope → offer ambulatory ECG. Do not offer a tilt test before the ambulatory ECG.
- For people with suspected carotid sinus syncope and for people with unexplained syncope who are aged 60 years or older, → offer carotid sinus massage as a first-line investigation.
 - ⇒ This should be conducted in a controlled environment, with ECG recording, and with resuscitation equipment available.
 - ⇒ Diagnose carotid sinus syncope if carotid sinus massage <u>reproduces syncope</u> due to marked bradycardia/asystole and/or marked hypotension.
 - ⇒ Do not diagnose carotid sinus syncope if carotid sinus massage causes <u>asymptomatic</u> transient bradycardia or hypotension

Tilt test

- ⇒ Do not offer a tilt test to people who have a diagnosis of vasovagal syncope on initial assessment.
- ⇒ For people with suspected <u>vasovagal syncope with recurrent episodes of TLoC</u> adversely affecting their quality of life, or representing a high risk of injury, → consider a tilt test <u>only to assess whether the syncope is accompanied by a severe cardioinhibitory response (usually asystole).</u>
- If a person has persistent TLoC, consider psychogenic <u>non-epileptic seizures (PNES)</u> or <u>psychogenic pseudosyncope</u> if:
 - the nature of the events changes over time
 - ⇒ there are multiple unexplained physical symptoms
 - ⇒ there are unusually prolonged events.

Driving

- ⇒ must not drive while waiting for a specialist assessment.
- ⇒ Following specialist assessment →report the TLoC event to (DVLA)

Implantable loop recorder (ILR)

- subcutaneous, single-lead, (ECG) monitoring device
- used for diagnosis in patients with recurrent unexplained episodes of palpitations or syncope,
- The device is typically implanted in the left parasternal region and is capable of storing ECG data automatically in response to a significant bradyarrhythmia or tachyarrhythmia or in response to patient activation.
- It is particularly useful either <u>when symptoms are infrequent</u> (and thus not amenable to diagnosis using short-term external ECG recording techniques) or when aggregate longterm data (eg, burden of AF) are required.

Vasovagal syncope (VVS)

• Vasovagal syncope (VVS) is the most common type of syncope.

Causes

- features suggestive of uncomplicated vasovagal syncope (the 3 'P's):
 - Posture prolonged standing, or similar episodes that have been prevented by lying down
 - ⇒ **P**rovoking factors (such as pain or a medical procedure)
 - common during dental procedures, mainly induced by pain (as the dentist started drilling).
 - ⇒ **P**rodromal symptoms (such as sweating or feeling warm/hot before TLoC).

Feature

- VVS is usually preceded by a prodrome of symptoms such as dizziness, nausea, and diaphoresis.
 - ⇒ The syncope lasts briefly, but nausea, warmth and sweating may persist for some time.
- Twitching and jerking are often seen with vasovagal or cardiac syncope, which can be differentiated from rhythmic jerking of all the limbs in tonic-clonic seizures.
- It is common to have jerking of limbs due to brain hypoxia.
- Incontinence of urine can occur, but not biting of the tongue.

Diagnosis

- Recover very guickly supports the diagnosis of syncope.
- · ECG is always normal.
- Tilt table test is a useful test to support the diagnosis
 - If structural heart disease is excluded and syncope is reproduced on tilt table testing along with fall in blood pressure and heart rate, then this is diagnostic of vasovagal syncope.

Treatment

- Midodrine may be indicated in patient with VVS refractory to life style management
 - ⇒ Midodrine is a prodrug of Desglymidodrine
 - ⇒ a sympathomimetic (alpha receptor agonist) that acts on the blood vessels to raise blood pressure.

Postural hypotension

- Causes: mnemonic (HANDI)
 - ⇒ H = Hypovolemia, Hypopituitarism (dehydration, bleeding)
 - ⇒ A = Addison's disease
 - ⇒ N = Neuropathy (autonomic due to diabetics, amyloidosis)
 - ⇒ D = Drugs (Vasodialators, TCA, antipsychotic, Diuretics etc.)
 - ⇒ I = Idiopathic orthostatic hypotension
- Management of postural hypotension
 - ⇒ if the standing BP is clearly acceptable (110 systolic), the most obvious first step is stopping the causative drug (eg: indapamide) and monitoring his blood pressure over the subsequent 2-4 weeks.
 - ⇒ If he still has significant postural hypotension then **the next steps** would be to add elastic stockings, **then** fludrocortisone.
 - ⇒ The history of pre-syncope is much more suggestive of changes in blood pressure rather than changes in blood glucose.

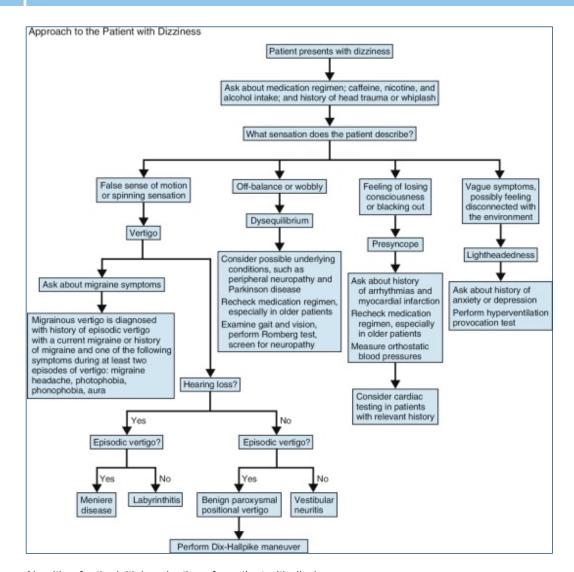
Vertigo & Dizziness

Clinical features of central versus peripheral vertigo

Chimour routures of contrar vortice peripheral vortige			
	Peripheral	Central	
Nystagmus Direction	Unidirectional, fast component toward the normal ear; never reverses direction	Sometimes reverses direction when patient looks in the direction of slow component	
Nystagmus Type	Horizontal with a torsional component, never purely torsional or vertical	Can be any direction	
Nystagmus Effect of visual fixation	Suppressed	Not suppressed	
Other neurologic signs	Absent	Often present	
Postural instability	Unidirectional instability, walking preserved	Severe instability, patient often falls when walking	
Deafness or tinnitus	May be present	Absent	

Dix-Hallpike maneuver for positional nystagmus: Findings in central versus peripheral vertigo

	Peripheral disorder	Central disorder
Latent period before onset of positional nystagmus	2 to 20 seconds	None
Duration of nystagmus	Less than 1 minute	Greater than 1 minute
Fatigability	Fatiguing with repetition	Non-fatiguing
Direction of nystagmus	Only one type, may change direction with gaze	May change direction with a given head position
Intensity of vertigo	Severe	Less severe, sometimes none



Algorithm for the initial evaluation of a patient with dizziness.

The HINTS exam: (Head Impulse, Nystagmus, Test for Skew)

- A three step physical exam testing oculomotor function (The HINTS exam) was able to differentiate between peripheral causes of vertigo and stroke with a <u>sensitivity of 100%</u>, and a specificity of 96%.
- Remember, the patient needs to be currently experiencing vertigo in order to perform the HINTS exam.

Head Impulse Test (HI)

- Method:
 - ⇒ Patient looks at your nose
 - ⇒ Hold skull (not jaw) firmly
 - ⇒ Slow movement to relax neck muscles
 - ⇒ Quick movement about 20 degree from lateral to midline
 - ⇒ Activate your biceps and forearm, not just wrists
 - ⇒ Random side tested
- Interpretation:
 - ⇒ In <u>peripheral vertigo</u> where the vestibulo-ocular reflex (VOR) reflex is impaired, rapid head rotation toward the affected side will cause the patients eyes to slowly move away from the target and force a corrective saccade (fast) back to the target.
 - ⇒ In central vertigo the VOR reflex remains intact.

Nystagmus (N)

- In peripheral vertigo:
 - ⇒ **uni**directional horizontal nystagmus with the fast phase beating away from the affected side.
- In central vertigo:
 - ⇒ vertical or rotational nystagmus, or bidirectional horizontal nystagmus where the fast phase changes directions.

Test for skew (TS)

- Method
 - ⇒ alternating covering the patients eyes while the patient fixes their gaze on a fixed target.
- Interpretation
 - ⇒ In central vertigo:
 - the patients sometimes have vertical misalignment of their eyes due to impaired gravity sensing. As the cover moves back and forth between the two eyes, the uncovered eye will correct its gaze to refocus on the target. This correction should be observed repeatedly as the cover moves back and forth.
 - ⇒ In peripheral vertigo:
 - no skew deviation.

In summary: The HINTS exam:

- **Peripheral** = Positive head impulse test, unidirectional nystagmus, no skew
- Central = Negative head impulse test, bidirectional, vertical or rotational nystagmus,

Sudden cardiac death

- In those aged greater than 35 years:
 - ⇒ The most common cause of sudden cardiac death is ischemic heart disease.
 - ⇒ Up to 80% of individuals who suffer sudden cardiac death have coronary heart disease.
- In those under the age of 35 years of age:
 - ⇒ HOCM is the most common cause of sudden cardiac death, coronary artery disease being the second most common cause.
 - ⇒ In competitive athletes <35 years of age HOCM is by far the most common cause of sudden cardiac death (prevalence is 1 in 500).
- Arrhythmogenic right ventricular dysplasia (ARVD)
 - ⇒ the second most common cause of sudden cardiac death in the young after HOCM.
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
 - ⇒ an autosomal dominant inherited cardiac disease
 - ⇒ prevalence of around 1:10,000.
- Brugada syndrome
 - ⇒ an autosomal dominant inherited cardiovascular disease.
 - ⇒ prevalence of 1:5,000-10,000.
 - ⇒ more common in Asians.

Exercise tolerance tests

Indications: Exercise tolerance tests (ETT, also exercise ECG) are used for a variety of indications:

- assessing patients with suspected angina however the 2010 NICE Chest pain of recent onset guidelines do not support the use of ETTs for all patients
- risk stratifying patients following a myocardial infarction
 - ⇒ the best predictor of mortality post-STEMI → exercise capacity
 - ⇒ Above average exercise capacity → good prognosis after a STEMI
- · assessing exercise tolerance
- risk stratifying patients with hypertrophic cardiomyopathy

Sensitivity and specificity of ETT: (high number of false positives and false negatives)

- ETT has a sensitivity of around 80% and a specificity of 70% for ischaemic heart disease. Thus, a negative test may not necessarily be true and further testing may be adviced.
 - Exercise ECG testing has a relatively high sensitivity but only moderate specificity for the diagnosis of CAD.
- Diagnostic accuracy is poor in women and this may relate to smaller heart size.

Heart rate

- maximum predicted heart rate = 220 patient's age
- the target heart rate is at least 85% of maximum predicted to allow reasonable interpretation of a test as low-risk or negative

Contraindications

- myocardial infarction less than 7 days ago
- unstable angina
- uncontrolled hypertension (systolic BP > 180 mmHg) or hypotension (systolic BP < 90 mmHg)
- Any condition where left ventricular output is reduced eg, aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM).

Abnormal baseline ECG (eg, bundle branch block patterns or left ventricular hypertrophy);
 these make interpretation of the ETT difficult.

Stop if:

- exhaustion / patient request
- 'severe', 'limiting' chest pain
- > 3mm ST depression
- > 2mm ST elevation. Stop if rapid ST elevation and pain
- systolic blood pressure > 230 mmHg
- systolic blood pressure falling > 20 mmHg
- attainment of maximum predicted heart rate
- heart rate falling > 20% of starting rate
- arrhythmia develops

Interpreting the exercise tolerance test

- The patient is normally considered to have been adequately 'stressed' if they achieve 85% or more of their maximum heart rate (calculated as 220 age in years for men and 210 age for women).
- If ECG criteria for inducible ischaemia (chest pain is not mandatory). The next step is
 → Coronary angiography
 - ⇒ this will define the coronary anatomy and give a better guide to prognosis.
- If an inadequate test was performed, further non-invasive investigations may be indicated, such as myocardial perfusion scanning, cardiac MRI, or stress echocardiogram.

Notes

- Beta-blockers and digoxin can interfere with the results so are usually stopped before the ETT.
 - ⇒ If ETT performed on beta blocker and there is an adequate rise in heart rate (85% of (220 age)) → so there is no indication for stopping beta blocker and repeat the test

Cardiac enzymes and protein markers

Myoglobin rises first following a myocardial infarction

Key points for the exam

- myoglobin is the first to rise
- CK-MB is useful to look for reinfarction as it returns to normal after 2-3 days (troponin T remains elevated for up to 10 days)

	Begins to rise	Peak value	Returns to normal		
Myoglobin	1-2 hours	6-8 hours	1-2 days		
CK-MB	2-6 hours	16-20 hours	2-3 days		
СК	4-8 hours	16-24 hours	3-4 days		
Trop T	4-6 hours	12-24 hours	7-10 days		
AST	12-24 hours	36-48 hours	3-4 days		
LDH	24-48 hours	72 hours	8-10 days		

Troponin

Troponin C: Binds to calcium to activate actin: myosin interaction

Troponin T: Binds to tropomyosin

Troponin I: Blocks or inhibits actin: myosin interaction

- Troponin is a component of thin filaments
- · Cardiac-specific marker with high sensitivity for myocardial necrosis
- The degree of elevation correlates with the size of the infarct and risk of mortality. Levels
 act as a prognostic factor following an acute coronary syndrome
- · Other causes of an elevated troponin are:
 - ⇒ Pulmonary embolism, Pulmonary hypertension
 - ⇒ Hypertension, Hypotension, especially with arrhythmias
 - ⇒ Hypertrophic obstructive cardiomyopathy, Myocarditis including Kawasaki's disease
 - ⇒ Sepsis, Burns, Trauma, Cardioversion, Rhabdomyolysis
 - ⇒ Subarachnoid haemorrhage and stroke
 - ➡ Infiltrative/autoimmune disorders including sarcoidosis, amyloidosis, haemochromatosis and scleroderma.
 - ⇒ Drugs including: Adriamycin, Herceptin and 5-fluorouracil.

CK-MB

- No longer commonly used clinically; has been replaced by cardiac troponin in the diagnosis
 of ACS
- CK-MB is more specific to cardiac tissue than total CK (but may also be due to skeletal muscle injury).
- Can be helpful for evaluating reinfarction because of its short half-life but is no longer commonly used
- The degree of elevation often correlates with the size of the infarct.

Serum creatine kinase

- Causes of high CK
 - ⇒ Mvocardial infarction
 - ⇒ Racial variant : serum CK activity in Afro-Caribbean people is often up to three times the upper limit of normal for white populations
 - ⇒ Hypothyroidism
 - ⇒ Heavy exercise
 - ⇒ Statins

Glycogen phosphorylase isoenzyme BB (GPBB)

- GPBB exists in heart and brain tissue.
- Rise significantly by three hours post mi. As such it is an appropriate marker for early cardiac muscle injury.
- Rise earlier than myoglobin
 - ⇒ GPBB levels increase 1–3 h after the event.
 - ⇒ Myoglobin levels increase significantly 2 h after ischaemia.

ECG: axis deviation

Normal axis

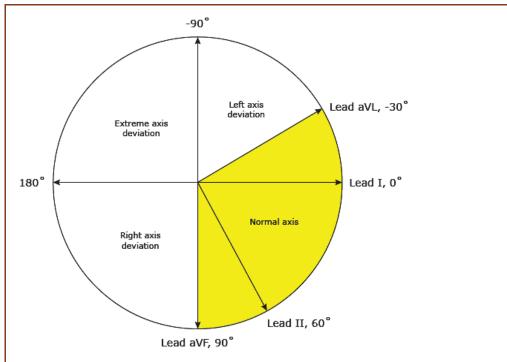
• between -30 and 90° (directed inferior and to the left)

Left axis deviation (LAD)

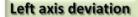
- Definition
 - ⇒ An axis between -30° and -90° (directed superior and to the left)
- Prevalence
 - ⇒ LAD (≥ 30 degrees) is the most common "abnormality" in adults occurring in over 8%.
- Causes of LAD:
 - ⇒ left ventricular hypertrophy
 - ⇒ left bundle branch block
 - ⇒ left anterior hemiblock
 - Marked LAD (≥ 45 degrees) is called left anterior hemiblock or left anterior fascicular block
 - ⇒ Wolff-Parkinson-White syndrome* right-sided accessory pathway
 - *in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation
 - ⇒ congenital: ostium **primum** ASD, tricuspid atresia, endocardial cushion defect
 - ⇒ Inferior wall myocardial infarction
 - ⇒ hyperkalaemia
 - ⇒ Normal variation (physiologic, often with age), minor LAD in obese people
 - ⇒ Mechanical shifts, such as expiration, high diaphragm (pregnancy, ascites, abdominal tumor)
 - ⇒ Emphysema
 - ⇒ Ventricular ectopic rhythms
- Recommendations: (If LAD is present):
 - ⇒ Exclude hypertension. (If borderline → ambulatory BP monitoring).
 - ⇒ check for borderline indicators of LVH (i.e., the voltage criteria and left atrial enlargement).
 - ⇒ Note whether diagnostic inferior Q waves are present since an inferior MI can cause LAD.

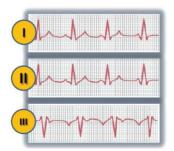
Right axis deviation (RAD)

- Definition
 - ⇒ An axis between 90° and 180° (directed inferior and to the right),
- · Causes of RAD:
 - ⇒ right ventricular hypertrophy
 - ⇒ right bundle branch block
 - ⇒ left posterior hemiblock
 - ⇒ Wolff-Parkinson-White syndrome left-sided accessory pathway
 - ⇒ ostium secundum ASD
 - ⇒ chronic lung disease → cor pulmonale
 - ⇒ pulmonary embolism
 - ⇒ Dextrocardia
 - ⇒ Ventricular ectopic rhythms
 - ⇒ Lateral wall myocardial infarction
 - ⇒ Normal variation (vertical heart with an axis of 90°).
 - normal in youngsters (less than 21 years of age), tall people, thin adults and athletes

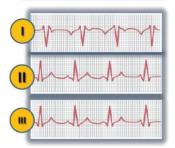


- If the QRS complex is positive (upright) in leads I and II, it falls between -30 and 90° and is normal, as indicated by the yellow area.
- If the QRS complex is **negative in I** and positive in aVF, there is **right axis deviation**.
- If the QRS complex is positive in I and negative in II, there is left axis deviation.
- If the QRS complex is negative in I and aVF, there is extreme axis deviation.





Right axis deviation



ECG: coronary territories

The table below shows the correlation between ECG changes and coronary territories:

Localization of myocardial infarct on ECG

	ECG changes	Coronary artery		
Anteroseptal	V1-V4	Left anterior descending (LAD)		
Inferior	II, III, aVF	Right coronary		
Anterolateral	V4-6, I, aVL	Left anterior descending (LAD) or left circumflex		
Lateral	I, aVL +/- V5-6	Left circumflex		
Posterior	Tall R waves V1-2	Usually left circumflex, also right coronary		

High lateral wall MI

- ST segment elevation in leads I and aVL → High lateral wall MI
- usually due to occlusion of the first diagonal branch of the left anterior descending artery, though occlusion of other arteries like branches of the left circumflex or a short left anterior descending artery may cause the same picture.

Postero-lateral MI → prominent R wave in lead V1 and ST depression in V1-V3 + ST elevation in leads V5 and V6.

Posterior MI (ESC guidelines 2017)

- posterior wall (now termed inferobasilar), usually supplied by the posterior descending artery a branch of the **right coronary artery** in 80% of individuals.
- isolated ST-segment depression \geq 0.5 mm in leads V_1 – V_3 represents the dominant finding. These should be managed as a STEMI.
- The use of <u>additional posterior chest wall leads</u> [elevation V₇–V₉ ≥ 0.5 mm (≥1 mm in men, 40 years old)] is recommended.

Left main stem (LMS)

- LMS occlusion typically presents dramatically with cardiogenic shock.
- ECG findings include ST elevation in aVR with diffuse ST depression in other leads.
- The presence of ST depression ≥ 1 mm in six or more surface leads, coupled with ST-segment elevation in aVR and/or V₁, suggests **multivessel ischemia** or **left main coronary artery obstruction**, particularly if the patient presents with haemodynamic compromise. (ESC guidelines 2017)

Which ECG changes may be seen earlier in ischaemia?

hyper-acute T-waves, which may precede ST-segment elevation.

ECG criteria for STEMI (ESC guidelines 2017)

- ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases:
 - ⇒ **Numbers of leads**: at least two contiguous leads with ST-segment elevation
 - ⇒ ST-segment elevation:
 - ≥ 2.5 mm in men < 40 years,
 - ≥ 2 mm in men ≥ 40 years, or
 - ≥ 1.5 mm in women in leads V₂–V₃ and/or
 - ≥ 1 mm in the other leads
 - ⇒ In patients with inferior MI, it is recommended to record right precordial leads (V₃R and V₄R) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction.
 - ⇒ Likewise, ST-segment depression in leads V_1 – V_3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation ≥ 0.5 mm recorded in leads V_7 – V_9 should be considered as a means to identify **posterior MI** (circumflex occlusion).

ECG: digoxin

ECG features

- down-sloping ST depression ('reverse tick')
- flattened/inverted T waves
- short QT interval
- arrhythmias e.g. AV block, bradycardia

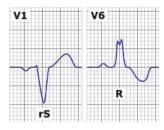
ECG: hypothermia

The following ECG changes may be seen in hypothermia

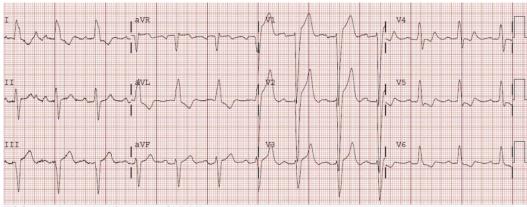
- bradycardia
- 'J' wave small hump at the end of the QRS complex
- first degree heart block
- long QT interval
- · atrial and ventricular arrhythmias

ECG: left bundle branch block

• The diagram below shows the typical features of left bundle branch block (LBBB):



- · The ECG would show:
 - ⇒ broad QRS complex (>120ms),
 - ⇒ tall R waves in the lateral leads (I, V5-6) and deep S waves in the right precordial leads (V1-3)
 - ⇒ usually leads to left axis deviation.
- One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW
 - William: in LBBB there is a 'W' in V1 and a 'M' in V6
 - MaRRoW: in RBBB there is a 'M' in V1 and a 'W' in V6

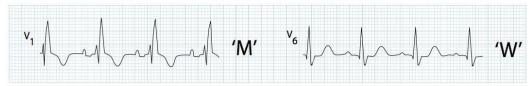


ECG showing typical features of LBBB

- · Causes of LBBB
 - ⇒ ischaemic heart disease
 - ⇒ hypertension
 - ⇒ aortic stenosis
 - ⇒ cardiomyopathy
 - ⇒ rare: idiopathic fibrosis, digoxin toxicity, hyperkalaemia

Right bundle branch block (RBBB)

- Patients with MI and right bundle branch block (RBBB) have a poor prognosis. (ESC guidelines 2017)
 - ⇒ It may be difficult to detect transmural ischaemia in patients with chest pain and RBBB.
 - ⇒ Therefore, persistent ischaemic symptoms occur in the presence of RBBB → primary PCI strategy (emergent coronary angiography and PCI if indicated) should be considered



Trifascicular block

The evidence of trifascicular block (RBBB, LAD and prolongation of the PR interval) in the context of dizziness and collapses. This is an indication for dual chamber (DDDR) pacing for likely complete heart block.

- Trifascicular block is not strictly an ECG diagnosis but is a term used for the combination of:
 - 1. right bundle branch block,
 - 2. left hemiblock (typically left anterior hemiblock (LAHB)) (LAHB is diagnosed because the net QRS deflection in lead II is negative).
 - 3. long PR interval.
- the site of the lesion →AV node and Purkinje fibres

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- The most common pattern referred to as "trifascicular block" is the combination of bifascicular block with 1st degree AV block.
- It implies that the bundle branches (Purkinje fibres) are blocked in the right bundle and one
 of the left hemibundles.
- The 'third' bundle is also delayed or partially blocked hence the name. However, the delay (long PR interval) is usually at the AV node.
- Clinically it means there is extensive disease of the conduction system and, in a patient such as this, would be an indication for permanent pacemaker.

ECG: normal variants

The following ECG changes are considered normal variants in an athlete:

- · sinus bradycardia
- iunctional rhythm
- first degree heart block
- Wenckebach phenomenon

ECG: PR interval

Causes of a prolonged PR interval

- idiopathic
- · ischaemic heart disease
- digoxin toxicity
- hypokalaemia: hyperkalaemia can rarely cause a prolonged PR interval, but this is a much less common association than hypokalaemia
- rheumatic fever
- · aortic root pathology e.g. abscess secondary to endocarditis
- Lyme disease
- sarcoidosis
- · myotonic dystrophy
- A prolonged PR interval may also be seen in athletes

short PR interval is seen in Wolff-Parkinson-White syndrome

ECG: ST depression

Causes of ST depression

- secondary to abnormal QRS (LVH, LBBB, RBBB)
- ischaemia
- digoxin
- hypokalaemia
- syndrome X

T wave

- The T wave should be analyzed for:
 - 1) orientation: upgoing, downgoing (inverted) or biphasic
 - 2) concordance with QRS
 - Concordant: (normal) both QRS and T wave are on the same direction (upgoing or downgoing) (downgoing is common in aVR for normal ECG's)
 - Discordant: (abnormal) QRS is upgoing, T wave is downgoing or vice versa
 - 3) morphology (size and shape)

Biphasic T wave





- Biphasic T waves can be "up then down", or "down, then up".
- There are 2 causes of biphasic T waves:
 - ⇒ Ischemia
 - Wellens' syndrome (type II):
 - Two types of Wellens' syndrome are identified:
 - 1. Type I: The most common (75% of cases), characterised by deep negative T waves in V2–V3 and often in V4.
 - Type II: less common (one third of patients) ,present with biphasic T waves in V2–V3
 - pathognomonic of critical stenosis of the proximal left anterior descending coronary artery (LAD)
 - It is also known as the "widow maker" sign because of the high risk of an acute coronary syndrome within days/weeks if it is untreated
 - ⇒ Hypokalaemia

Q waves

- A Q wave is any negative deflection that precedes an R wave on the ECG.
- The evolution of Q waves is the most suggestive of an infarct. (more specific than ST elevation and cardiac enzyme for MI)
 - ⇒ the most specific for a diagnosis of myocardial infarction
- Small Q-waves are normal in most leads, and they can be prominent in leads III and aVR as a normal variant but should not be seen in leads V1-V3.
- They are considered pathological if they are:
 - ⇒ more than 1mm wide,
 - ⇒ more than 2mm deep,
 - ⇒ more than 25% of the depth of the QRS complex, or
 - ⇒ seen in leads V1-V3.
- Such pathological Q-waves usually indicate prior full thickness myocardial infarct.

ECG: ST elevation (STE)

Causes of ST elevation

- myocardial infarction
- pericarditis
- · normal variant 'high take-off'
- left ventricular aneurysm
- Prinzmetal's angina (coronary artery spasm)
- · rare: subarachnoid haemorrhage, part of spectrum of changes in hyperkalaemia

Early repolarization

Definition

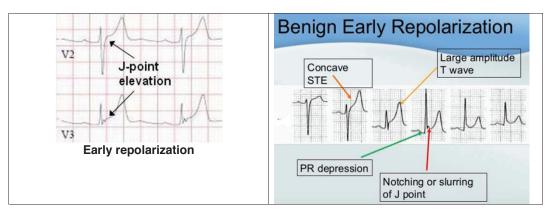
⇒ It appears as mild ST segment elevation (appears like an elevated "J point.") that can be diffuse; however, it is more prominent in the precordial leads.

Causes

- ⇒ common finding in young, healthy individuals.
- ⇒ Prevalence: occurs in up to 13% of the general population

Differential diagnosis

- ⇒ Early repolarization (benign finding)
- ⇒ acute myocardial infarction (convex and not diffuse)
- ⇒ pericarditis
 - The ST elevation seen in early repolarization is very similar: <u>diffuse and</u> concave upward.
 - Three things may help to distinguish pericarditis from early repolarization:
 - 1) The ratio of the T wave amplitude to the ST elevation should be > 4 if early repolarization is present. In other words, the T wave in early repolarization is usually 4 times the amplitude of the ST elevation. Another way to describe this would be that the ST elevation is less than 25% of the T wave amplitude in early repolarization.
 - The ST elevation in early repolarization resolves when the person exercises.
 - 3) Early repolarization, unlike pericarditis, is a benign ECG finding that should not be associated with any symptoms.



QT Interval

Definition

The QT interval is the time between the onset of the QRS complex and the end of the T wave.

Physiology

- It represents the ventricular diastole
- QRS corresponds with ventricular depolarization (when it contracts) and T wave corresponds with ventricular repolarization (when contraction stops).

Which phase of the cardiac cycle shortens the most with increasing heart rate?

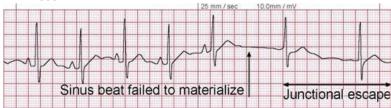
- it is diastole.
 - Diastole is usually the longest portion of the cardiac cycle, and its duration diminishes the most (more than the reduction seen in the duration of systole) with increasing heart rate.

Which ECG interval will show the greatest reduction during ECG stress test?

QT interval

ECG: Junctional escape rhythm

- Junctional escape rhythm describes an abnormal heart rhythm that arises within the AV node or from an adjacent area.
- There is a slow, regular pulse rate.
- Common after a pause in the underline rhythm
- ECG shows absent P waves, narrow QRS complexes, and a heart rate of 40 to 60 bpm.
- Retrograde P waves, which appear immediately before or after the QRS complex may be seen.



Cardiac amyloidosis

Amyloid

- Low-voltage ECG
- Speckled pattern on echo

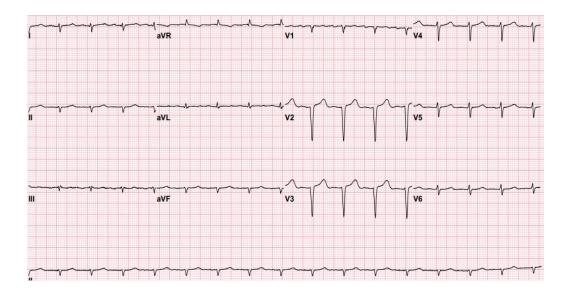
Features

- most commonly presents as restrictive cardiomyopathy.
- clinical findings are those of right heart failure, i.e. jugular venous distension and peripheral oedema.
- orthopnoea and paroxysmal nocturnal dyspnoea are typically absent.
- systolic dysfunction (In more advanced stages,)
- Postural hypotension can occur as a result of poor ventricular filling or associated autonomic neuropathy.

Investigations

- ECG
 - ⇒ The combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.
- Echo
 - ⇒ echocardiographic abnormalities include atrial dilatation, thickened interatrial septum, diastolic dysfunction and small-volume ventricles.
 - ⇒ The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of the myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases.
 - ⇒ 'global speckled' pattern on echo.
- The history of rheumatoid arthritis and the echocardiographic finding of bi-atrial dilatation, ventricular hypertrophy and a speckled appearance to the myocardium make amyloidosis the most likely underlying cause.
- Digoxin is contraindicated in amyloid patients as the digoxin binds irreversibly to the amyloid fibrils.

The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudo-infarction pattern).



ECG: Wrong leads

- They are normally labelled red (right arm) and yellow (left arm). The other leads are green (left leg) and black (right leg).
- If the wires to the right and left arms have been accidentally swapped over → It gives the
 appearance of abnormal T wave inversion in the lateral leads I and aVL.
- The clue to recognising it is the <u>inverted P waves in lead I</u> and the <u>upright aVR</u> which are both highly unusual for a 12-lead ECG.
 - ⇒ The correct course of action → Repeat the ECG again

Early repolarization variant

Mechanism

It is expresses as an early uptake of the ST segment before the descending limb of the R
wave has reached the baseline.

Features

- benign but often alarming ST segment elevation
 - ⇒ Classically the ST segment elevation during early exercise returns to normal as heart rate increases further
- · It is common in black males
- Clinical evaluation is entirely normal
- ST elevation is usually seen in the precordial leads

ECG: U wave

Causes of prominent U waves are:

- Hypokalaemia
- Cardiovascular drugs, e.g. digitalis, quinidine, amiodarone
- Psychotropic drugs, e.g. phenothiazines, tricyclic antidepressants.

Cardiac catheterisation and oxygen saturation levels

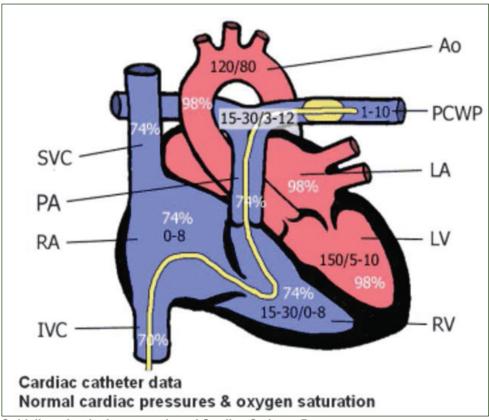
 Questions regarding cardiac catheterisation and oxygen saturation levels can seem daunting at first but a few simple rules combined with logical deduction can usual produce the answer.

Let's start with the basics:

- deoxygenated blood returns to the right side of the heart via the superior vena cava (SVC) and inferior vena cava (IVC). It has an oxygen saturation level of around 70%. The right atrium (RA), right ventricle (RV) and pulmonary artery (PA) normally have oxygen saturation levels of around 70%
- the lungs oxygenate the blood to a level of around **98-100**%. The left atrium (LA), left ventricle (LV) and aorta should all therefore have oxygen saturation levels of 98-100%

Some examples:

Diagnosis & notes	RA	RV	РΑ	LA	LV	Aorta
Diagnosis & notes	nA	ΠV	FA	LA	LV	AUITA
Normal	70%	70%	70%	100%	100%	100%
Atrial septal defect (ASD)	85%	85%	85%	100%	100%	100%
The oxygenated blood in the LA mixes with the deoxygenated blood in the RA, resulting in intermediate levels of oxygenation from the RA onwards						
Ventricular septal defect (VSD)	70%	85%	85%	100%	100%	100%
The oxygenated blood in the LV mixes with the deoxygenated blood in the RV, resulting in intermediate levels of oxygenation from the RV onwards. The RA blood remains deoxygenated						
Patent ductus arteriosus (PDA)	70%	70%	85%	100%	100%	100%
Remember, a PDA connects the higher pressure aorta with the lower pressure PA. This results in only the PDA having intermediate oxygenation levels						
VSD with Eisenmenger's	70%	70%	70%	100%	85%	85%
PDA with Eisenmenger's	70%	70%	70%	100%	100%	85%
ASD with Eisenmenger's	70%	70%	70%	85%	85%	85%



Guidelines for the Interpretation of Cardiac Catheter Data

- Right-heart saturations do not exceed 75%. Saturations more than this are suggestive of a left-to-right shunt.
- Atrial septal defect (ASD): The oxygen saturation in the RA and SVC should be the same. But in ASD there is a step-up in oxygen saturation at the level of the RA. This can only result from the addition of oxygenated blood to the deoxygenated blood in the right heart circulation, that is, an abnormal connection between the right and left sides of the heart.

⇒ Primum ASD:

- The location of the step-up is suggestive of a primum defect since these lesions occur low down in the A-V septum, lying immediately above the atrioventricular valves.
- These lesions can affect the function of the anterior leaflet of the mitral valve, causing mitral regurgitation.
- high pressures of Right ventricular are more likely to occur with primum ASDs.
- Patent ductus arteriosus (PDA)
 - ⇒ unexpected step-up in oxygen saturation between the RV and PA.
 - high pulmonary artery pressures
 - ⇒ high wedge pressure.

- ⇒ The change in O₂ saturation between the ascending and descending aorta strongly suggests the presence of a patent ductus.
- ⇒ Unfortunately the extremely elevated right sided pressures are indicative of advanced disease, not amenable to surgical correction. In late disease the machinery murmur said to be characteristic of the disease may well not be audible.
- Left-heart saturations vary from 96–98%. Saturations less than this are suggestive of a right-to-left shunt.
- In right-to-left shunts, the arterial saturations do not change with inspired high-concentration oxygen.
- Ventricular septal defect (VSD)
 - ➡ There is a step-up in the oxygen saturation between the RA and RV. This can only occur when there is an abnormal connection between these two chambers, that is, via a VSD.
 - ⇒ This is confirmed by the raised right ventricular pressures.
 - **⇒ VSD** with Eisenmenger's syndrome
 - the pressures in the RV and PA are markedly elevated, but RA pressure is normal.
 - The left ventricular oxygen saturation is low, which raises the possibility of a right to left cardiac shunt mixing desaturated RV blood with LV saturated blood (due to right ventricular pressures exceeding left ventricular pressure).
 - ⇒ post-MI VSD and papillary rupture are difficult to distinguish clinically.
 - The diagnosis is established by demonstration of a left to right shunt.
 - ❖ if there is a step-up in the oxygen saturation between the RA and PA → VSD
 - ❖ if there is no step-up, → papillary muscle rupture.
- Fallot's tetralogy
 - VSD: step-down in oxygen saturation between LA and LV, indicating right to left shunt at the level of the ventricles.
 - Pulmonary stenosis: there is ↑mmHg gradient across the pulmonary valve (RV systolic PA systolic).
 - 3. **RVH**: Right ventricular pressures are high and there is a right to left shunt, which indicated by the oxygen saturations.
 - 4. Over-riding aorta:
 - there is a further step-down in oxygen saturation between the LV and aorta.
 - This could occur in either Fallot's or with a patent ductus arteriosus with right to left shunting.
 - However, given the other features of Fallot's, this is most likely to be caused by an over-riding aorta with reduced saturations due to a mixture of deoxygenated blood from the RV entering the left heart circulation.
 - The over-riding aorta recieves a mixture of blood from the left and right ventricles as is formed above a VSD.
- Pulmonary hypertension does not occur in Fallot's tetralogy due to narrowing of the right ventricular outflow tract/ subpulmonary valve stenosis.
- A VSD with a right-to-left shunt and pulmonary stenosis can be differentiated from Fallot's tetralogy by examining the oxygen saturation in the left ventricle and the ascending aorta.
 - ⇒ In the case of a VSD, the saturations in the left ventricle and the aorta will both be low and very similar.

- □ In the case of Fallot's tetralogy, the aortic oxygen saturation will be much lower than the oxygen saturation in the left ventricle because the right ventricle pumps most of the deoxygenated blood into the overriding aorta.
- A pulmonary artery pressure exceeding 35 mmHg is suggestive of pulmonary hypertension.
- A pressure drop of more than 10 mmHg across the aortic or pulmonary valve is suggestive
 of aortic or pulmonary stenosis, respectively.
- The diagnosis of mitral regurgitation cannot be made unless you are given the PCWP 'v-wave'. A v-wave higher than 20 mmHg is highly suggestive of mitral regurgitation.
- The right and LVEDP and the left and right atrial pressures are roughly equal in pericardial constriction
- When interpreting right heart catheter data, remember the saturation should decrease gradually as the venous blood reaches the pulmonary capillary wedge saturation, which should be equal to arterial blood.
- In Ebsteins anomaly there should be elevated RA pressure due to significant tricuspid regurgitation.
- Hypertrophic cardiomyopathy
 - Left ventricular pressures are high with a steep drop-off between the LV and aortic systolic pressures.
- Anomalous pulmonary venous drainage to SVC
 - ⇒ normally oxygenation in the superior vena cava should always be lower than the inferior vena cava, due to the high oxygen demands from the brain.
 - ⇒ If SVC sats is markedly higher than the IVC, sugest a diagnosis of <u>anomalous pulmonary</u> <u>venous drainage</u> of more highly oxygenated blood into the SVC (left to right shunt).

What is meaning of "valve gradient"?

- The valve's gradient describes the severity of the narrowing of the valve by the increase in pressure behind it.
- It helps to measure the amount of blood that is able to pass through the valve.
- It also indicates whether the "velocity" (or speed of movement) of the blood flow is increased because of the increased pressure behind the narrowed valve.

Diagnosis of tricuspid stenosis

 mean gradient by echocardiogram or cardiac catheterisation of 2 mmHg or greater, but is usually found to be >7 to 10 mmHg in severe TS

Diagnosis of pulmonary hypertension

 If the pulmonary arterial pressure is greater than the normal one-fifth of systolic measurements → pulmonary hypertension is present.

Diagnosis of right ventricular failure

- The right atrial pressure is grossly elevated, with a normal wedge pressure.
 - ⇒ Normal right atrial pressure = (4–8) mmHg.
 - ⇒ Normal indirect left atrial mean pressure (wedge) = (5–10) mmHg.
 - normal wedge pressure excludes acute left ventricular failure or acute mitral regurgitation.

Diagnosis of aortic stenosis

- a greater than 25mmHg gradient across the aorta valve, demonstrating moderate aortic stenosis.
- systolic gradient of ↑ mmHg across the aortic valve (LV systolic pressure aortic systolic pressure), indicating critical aortic stenosis.
- Hypertrophic cardiomyopathy may result in similar pressure differences, but given the clinical information, aortic stenosis is far more likely than hypertrophic obstructive cardiomyopathy (HOCM) in an old patient.
- A guide to determining the severity of aortic stenosis is given below:

Severity of aortic stenosis	Severity Valve area (cm²)	Mean gradient (mmHg)
Mild	>1.5	<25
Moderate	1.0-1.5	25-50
Severe	<1.0	>50
Critical	<0.7	>80

Diagnosis of mitral stenosis

- A normal mitral valve expects less than 5mmHg pressure difference.
- Using these inferences, the mitral valve gradient is calculated by the capillary wedge
 pressure of mmHg (same as the left atrial pressure) minus the diastolic left ventricular
 pressure of mmHg: the mmHg difference more than 5 demonstrates mitral stenosis.
- The PCWP is equal to the LVEDP. When the PCWP exceeds the LVEDP, the diagnosis of mitral stenosis should be considered.
- The gradient across the mitral valve (LA pressure LV end diastolic pressure); it is usual to use the PCWP as a surrogate for LA pressure.
- There is also evidence of right ventricular hypertrophy, with markedly elevated RV pressures due to secondary pulmonary hypertension.
- The severity of mitral stenosis can be graded:

Severity of mitral stenosis	Severity Valve area (cm²)	Gradient (mmHg)
Mild	1.6-2.0	<5
Moderate	1.0-1.5	5-10
Severe	<1.0	>10

Aortic incompetence

- wide pulse pressure in the aorta
- high left ventricular end-diastolic pressure (LVEDP).
 - ⇒ LVEDP greater than 20 mmHg is suggestive of irreversible LV dysfunction.
- All left heart valve diseases can ultimately cause elevated right heart pressures

Coarctation of the aorta

There is a steep systolic gradient between the left ventricle and the femoral artery

Pulmonary artery floatation catheter findings:

- if the pulmonary artery occlusion pressure is low with a relatively low cardiac index, suggesting the patient is hypovolaemic, even in spite of high right atrial pressure.
 - \Rightarrow A fluid challenge should be performed, and values re-measured to assess response.
 - ⇒ In a fluid replete patient, the occlusion pressure would be higher (usually >13 mmHg)
- if the Pulmonary artery occlusion pressure is high and cardiac index low (i.e. <2.5 L/min/m²) this would be more suggestive of cardiogenic shock.

Pulmonary artery floatation catheter findings:

- Low pulmonary artery occlusion pressure + low cardiac index → hypovolaemia
- High pulmonary artery occlusion pressure + low cardiac index → cardiogenic shock

Hyperthyroidism and cardiac catheterisation:

- Cardiac catheterisation requires the use of an iodine-containing contrast.
- This may worsen hyperthyroidism caused by toxic multinodular goitre, whereas it may improve the symptoms in patients with Grave's disease (Wolff–Chaikoff effect).
- The most reliable diagnostic method is a radionuclide (99Tcm, 123I or 131I) scan of the thyroid, which will distinguish the diffuse, high uptake of Grave's disease from nodular thyroid disease.
- If a toxic multinodular goitre or toxic adenoma is detected, the patient should receive an antithyroid drug before undergoing catheterisation.
- The antithyroid medication must be continued for at least 2 weeks after the procedure.

Pulmonary capillary wedge pressure

- Pulmonary capillary wedge pressure (PCWP) is measured using a balloon tipped Swan-Ganz catheter which is inserted into the pulmonary artery.
- The pressure measured is similar to that of the left atrium (normally 6-12 mmHg).
- The PCWP provides an indirect measurement of the left atrial pressure, and since the left atrial pressure is increased, the PCWP will also be increased.
- One of the main uses of measuring the PCWP is determining whether pulmonary oedema is caused by either heart failure or acute respiratory distress syndrome.
- In many modern ITU departments PCWP measurement has been replaced by non-invasive techniques.

Which method is an appropriate of measuring adequate intravascular filling?

- PiCCO (pulse contour cardiac output)
 - PiCCO gives indications of cardiac output, extravascular lung water, intravascular filling and only requires a central line and a PiCCO femoral arterial line and as such is relatively simple to use.

<u>Cardiac imaging: non-invasive techniques excluding</u> <u>echocardiography</u>

Nuclear imaging

- These techniques use radiotracers which are extracted by normal myocardium.
- Examples include:
 - ⇒ Thallium
 - Nuclear isotopes are picked up by the Na/K ATPase of normal myocardium.
 - If cardiac tissue is alive and perfused, it will pick up the nuclear isotope.
 - To the myocardium, thallium looks like potassium.
 - Decreased uptake = Damage
 - ⇒ technetium (99mTc) sestamibi:
 - a coordination complex of the radioisotope technetium-99m with the ligand methoxy-iso-butyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
 - ⇒ fluorodeoxyglucose (FDG):
 - used in Positron Emission Tomography (PET) scans
 - Cardiac PET is predominately a research tool at the current time

SPECT

- The primary role of SPECT is to assess myocardial perfusion and myocardial viability.
- Two sets of images are usually acquired. First the myocardium at rest followed by images
 of the myocardium during stress (either exercise or following adenosine / dipyridamole).
- By comparing the rest with stress images any areas of ischaemia can classified as reversible or fixed (e.g. Following a myocardial infarction).

MUGA

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- radionuclide (technetium-99m) is injected intravenously
- the patient is placed under a gamma camera
- may be performed as a stress test
- can <u>accurately measure left ventricular ejection fraction</u>.
- Typically used before and after cardiotoxic drugs are used

Cardiac Computed Tomography (CT)

- Cardiac CT is useful for <u>assessing suspected ischaemic heart disease</u>, using two main methods:
 - **⇒** calcium score:
 - there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischaemic events.
 - Cardiac CT can quantify the amount of calcium producing a 'calcium score'
 - ⇒ contrast enhanced CT:
 - allows visualisation of the coronary artery lumen
- If these two techniques are combined cardiac CT has a very high negative predictive value for ischaemic heart disease.
- The updated NICE guidelines recommends that **cardiac CT** is the <u>first-line investigation</u> for patients presenting with <u>new-onset chest pain due to suspected CAD</u>.

Cardiac MRI

- Cardiac MRI (commonly termed CMR) has become the gold standard for providing structural images of the heart.
- It is particularly **useful in**:
 - ⇒ assessing congenital heart disease.
 - ⇒ determining right and left ventricular mass and
 - ⇒ differentiating forms of cardiomyopathy.
 - Myocardial perfusion can also be assessed following the administration of gadolinium.
- Currently CMR provides limited data on the extent of coronary artery disease.

Mitral stenosis (MS)

Pathophysiology

- MS → mechanical obstruction of blood flow into the left ventricle (LV) → limited diastolic filling of the LV (↓ end-diastolic LV volume) → decreased stroke volume → decreased cardiac output (forward heart failure)
- MS → ↑left atrial pressure → backup of blood into lungs → ↑ pulmonary capillary pressure
 → cardiogenic pulmonary edema → pulmonary hypertension → backward heart failure and
 right ventricular hypertrophy

Causes

- Common → Rheumatic fever
 - ⇒ Rheumatic valve disease is increasing uncommon in the UK, but can still be seen in other parts of the world.
 - ⇒ The physiological stress of pregnancy can exacerbate the features of rheumatic mitral stenosis.
- Rare
 - ⇒ Calcification of the mitral valve annulus
 - ⇒ Autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis
 - ⇒ Congenital
 - ⇒ Mucopolysaccharidoses
 - ⇒ carcinoid

Features

- Malar flush: Mauve discoloration of the cheeks due to low cardiac output and systemic vasoconstriction
- Dyspnea
- Low volume pulse
- · Tapping apex beat
- Auscultation
 - ⇒ Loud first heart sound (S1)
 - ⇒ Mid-late diastolic murmur (with pre-systolic accentuation)
 - heard best at the 5th left intercostal space at the midclavicular line (the apex) in expiration.
 - ⇒ Opening snap
 - A high frequency, early to mid-diastolic sound, heard after S2
 - suggests that the mitral valve is mobile
 - opening snap is not heard when the mitral valve is heavily calcified
 - the high left atrial pressure → rapid reversal of anterior mitral valve leaflet towards the left ventricle in early diastole lead to early diastole sound.

Complications

- Compression by the enlarged left atrium

 - \Rightarrow Compression of the recurrent laryngeal nerve \rightarrow Hoarseness (known as Ortner syndrome.)
- Atrial fibrillation
 - ⇒ Embolic disease (e.g., stroke, mesenteric ischemia)
 - ⇒ Patients with mitral stenosis often develop acute heart failure following the onset of atrial fibrillation.
- · Leads to left atrial enlargement, but the left ventricle is usually small.
- Right heart failure (paroxysmal nocturnal dyspnea, orthopnea, lower limb pitting edema, bibasilar rales)
- Hemoptysis

Mechanism of opening snap earlier in worsening MS

The mitral valve opens when LA pressure > LV pressure. Worse MS = Higher LA pressure.
 Higher LA pressure pushes the mitral valve open earlier.

Features of severe MS

- length of murmur increases
- opening snap becomes closer to S2. (shorter interval between S2 and opening snap)
 - ⇒ opening snap is characteristically lost with heavy valvular calcification
- high transvalvular pressure gradient and high blood flow velocity.

Investigations

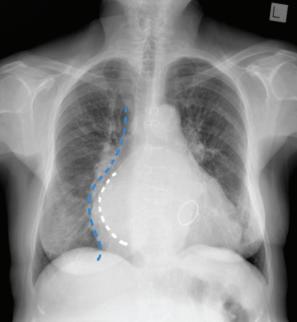
- Transthoracic echocardiography (TTE)
 - ⇒ TTE is the most important test for diagnosing and guiding the treatment of mitral stenosis.
 - ⇒ Characteristic findings include:
 - Reduced mitral valve area (MVA): ≤ 1.5 cm2 is considered to be severe MS
 - Thickened, calcified leaflets with commissural fusion
 - RV dilation
 - LA enlargement
 - Evidence of pulmonary hypertension

Chest x-ray

- ⇒ Left atrial enlargement may be seen
 - The main bronchi appear elevated and have > 90% angulation (splayed).
 - Straightening or convexity of the left cardiac border
 - Double density sign (the silhouette of the enlarged left atrium appears near that of the right atrium.)
- □ Cardiomegaly
- ⇒ Pulmonary congestion

• ECG

- ⇒ Often normal
- ⇒ Characteristic findings include:
- ⇒ Left atrial enlargement/P mitrale
- ⇒ Atrial fibrillation
- ⇒ Right ventricular hypertrophy (e.g., right axis deviation, dominant R wave in lead V1)



Chest x-ray from a patient with mitral stenosis. This patient has had a sternotomy and a prosthetic mitral valve. There is splaying of the carina with elevation of the left main bronchus, a **double right heart border** and **cardiomegaly**. The features are those of left atrial enlargement. Although the entire heart is enlarged, a **double contour** is seen through the right side of the heart. The more medial line is the enlarged left atrium (white dotted line) and the heart border is more lateral (blue dotted line).

Management

- · Asymptomatic: echocardiography follow-up
 - ⇒ every 3 to 5 years if the mitral valve area (MVA) is >1.5 cm²
 - ⇒ every 1 to 2 years if the MVA is 1.0 to 1.5 cm²
 - \Rightarrow once per year if the MVA is <1.0 cm².
- · Symptomatic with severe MS
 - ⇒ 1st line: transcatheter valvotomy : in patients with favorable valve morphology
 - ⇒ 2nd line: surgical mitral valve replacement: if transcatheter valvotomy is unsuitable.

Indications for surgical mitral valve replacement

- Unfavorable anatomy for transcatheter valvotomy (Percutaneous mitral valve balloon commissurotomy)
- Presence of thrombus in the left atrium
- Mixed valvular disease (e.g., severe MR, tricuspid disease)

Mitral stenosis in pregnancy

- Overview
 - ⇒ MS is poorly tolerated in pregnancy due to volume overload.
 - ⇒ Pregnancy can unmask previously undiagnosed obstructive valvular heart disease. The symptoms may developed in the second trimester, when the demand for cardiac output increases by around 70%.
- Treatment
 - ⇒ **Medical therapy** for mild symptoms (beta blockers and/or diuretics)
 - Percutaneous mitral balloon valvuloplasty (PMBV) should be carried out for severe mitral stenosis in patients who remain symptomatic despite medical therapy.
 - ⇒ Symptomatic patients with moderate to severe MS (mitral valve area ≤1.5 cm2) should undergo intervention, preferably percutaneous balloon mitral valvotomy, before pregnancy.
 - ⇒ Vaginal delivery with assisted second stage is the preferred mode of delivery with caesarian delivery generally reserved for obstetric reasons.

Mitral regurgitation (MR)

Valvular anatomy

- left atrial enlargement can result in mitral regurgitation by affecting which leaflet?
 - ⇒ posterior leaflet
 - anterior leaflet is not affected, because of its attachment to the root of the aorta.

Pathology

Myxomatous degeneration (the most common cause of MR in UK).

Risk factors and aetiology

- MR associated with Marfan syndrome and Ehlers-Danlos syndrome.
- cardiac complication seen 3-14 days <u>post-myocardial infarction</u> that occurs due to papillary muscle rupture.

Features

- Symptoms
 - ⇒ dyspnoea, usually on exertion, → decreased exercise tolerance.
 - ⇒ palpitations,

- Signs
 - soft S1, split S2
 - pan-systolic murmur
 - Typically presents as a holosystolic blowing murmur at the apex, radiating to axilla.
 - intensified by isometric exercise and thus helps to differentiate it from other systolic murmurs.
 - Sudden standing and amyl nitrite <u>decrease</u> the murmur.

Diagnosis

Transthoracic echo is the diagnostic test of choice

Which feature suggests more severe mitral regurgitation?

 As mitral regurgitation becomes more severe, the left ventricle enlarges, and the apex beat displaces, and a systolic thrill can develop.

Management

- asymptomatic chronic MR:
 - ⇒ left ventricular ejection fraction >60% and/or left ventricular end-systolic diameter <45 mm → (ACE) inhibitors + beta-blockers</p>
 - ⇒ left ventricular ejection fraction 60% or less and/or left ventricular end-systolic diameter 45 mm or more → surgery
- symptomatic chronic MR
 - ⇒ left ventricular ejection fraction 30% or more → surgery + medical treatment (ACE inhibitors, beta-blockers, and diuretics.)
 - ⇒ left ventricular ejection fraction <30% → medical treatment
 - intra-aortic balloon counterpulsation in severe acute cases

Mitral valve prolapse (MVP)

Epidemiology

- common, occurring in around 5-10 % of the population.
- the most common valvular defect in the United States
- more common in females.

Causes

- usually idiopathic
- inherited in an autosomal dominant fashion.
- may be associated with:
 - ⇒ congenital heart disease: PDA, ASD
 - ⇒ cardiomyopathy
 - ⇒ Turner's syndrome
 - ⇒ Marfan's syndrome,
 - ⇒ Fragile X
 - ⇒ osteogenesis imperfecta
 - ⇒ pseudoxanthoma elasticum
 - ⇒ Wolff-Parkinson White syndrome
 - ⇒ long-QT syndrome
 - ⇒ Ehlers-Danlos Syndrome
 - ⇒ polycystic kidney disease
 - ⇒ 15-40% of people with **panic disorder** have associated mitral valve prolapse.

Features

The late systolic murmur with mid systolic click is indicative of mitral valve prolapse where the posterior leaflets bulge during systole.

- atypical chest pain (the most common symptom)
- palpitations
- dyspnea, exercise intolerance,
- dizziness or syncope,
- panic and anxiety disorders.
- mid-systolic click (occurs later if patient squatting)
- late systolic murmur (longer if patient standing) heard best at the apex

Complications

- · mitral regurgitation,
- arrhythmias (including long QT),
- emboli,
- sudden death

Treatment

- Mild to moderate mitral regurgitation
 - ⇒ follow-up in clinic with repeat echocardiograms to monitor progression.
- Mitral valve replacement is only indicated in:
 - ⇒ severe mitral regurgitation or
 - ⇒ if there are signs of concomitant LV compromise (reduced ejection fraction or new dilatation of the LV).
- If a surgical mitral valve replacement are indicated, coronary angiogram should be part of the pre-op work-up for potential concomitant coronary artery bypass grafting.

Aortic dissection

Aortic dissection

- type A ascending aorta control BP(IV labetalol) + surgery
- type B descending aorta control BP(IV labetalol)
- It is most common between the ages of 50-70, being rare below the age of 40.

Stanford classification

- type A Ascending aorta, (immediately above of the aortic valve) → 2/3 of cases
- type B descending aorta, (after the aorta arch) distal to left subclavian origin, 1/3 of cases

DeBakev classification

- type I originates in ascending aorta, propagates to at least the aortic arch and possibly beyond it distally
- type II originates in and is confined to the ascending aorta
- type III originates in descending aorta, rarely extends proximally but will extend distally

Associations

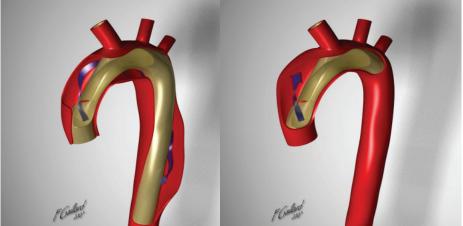
- hypertension (The most common risk factor)
- trauma (direct blunt chest trauma)
- collagens: Marfan's syndrome, Ehlers-Danlos syndrome
- · bicuspid aortic valve
- Turner's and Noonan's syndrome
- pregnancy
- syphilis
- Drugs (such as cocaine)

Complications of backward tear

- aortic incompetence/regurgitation
- MI: inferior pattern often seen due to right coronary involvement

Complications of forward tear

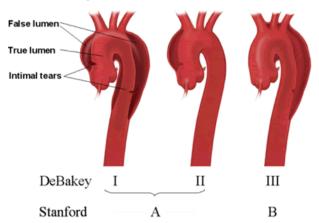
- unequal arm pulses and BP
- stroke
- · renal failure



Stanford type A / DeBakey type I

Floring

Stanford type A / DeBakey type II



Anatomy and Classification of Aortic Dissection

Stanford type B / DeBakey type III

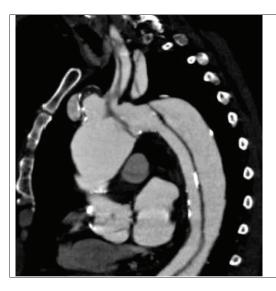
Investigations

- The best investigation is a CT chest with IV contrast (CT aortogram) because the IV contrast will be able to best demonstrate the size and extent of the false lumen.
- Chest X-ray:
 - ⇒ is a useful **first line** investigation because its readily available it is, and useful for ruling out many other conditions.
 - ⇒ The chest X-ray may show a widened mediastinum (greater than 8 cm)
 - ⇒ but unfortunately, it is not a sensitive or specific investigation as 20% of patients present with normal chest X-ray and there are many causes of a widened mediastinum.

- ⇒ Looking for a separation of the intimal calcification from the outer aortic soft tissue border by 10 mm is an indication of the presence of a dissection.
- In a man with low blood pressure and vague abdominal pain, always be mindful of the possibility of dissection or aneurysmal rupture.
- Occasionally, there is involvement of the right coronary artery in the dissection process giving rise to the acute electrocardiographic changes.
- MRI has the best sensitivity (98%) and specificity (98%) for aortic dissection.

Whilst an echocardiogram might identify disruption of the aortic root in a backwards tear, it
would not identify more distal aortic pathology.





This computerised tomography (CT) scan demonstrates an obvious **flap in the thoracic aorta indicating aortic dissection.** The flap is in the middle of the descending aorta (the dark line) which separates the true lumen anteriorly from the intimal flap posteriorly. The aortic regurgitant murmur would alert the examiner to this and mediastinal widening may be seen on x ray.

Differential diagnosis

- . Myocardial infarction and aortic dissection: an important differential diagnosis
 - ⇒ The ECG changes of inferior myocardial infarct suggest that the aneurysm has dissected the right coronary artery at its ascending aortic ostium.
 - ⇒ An inferior myocardial infarct is high in the differential; however thrombolysis will kill a patient with an aortic dissection. (delayed diagnosis and surgical treatment)
 - ⇒ up to 85% of patients with dissections may not receive appropriate medical treatment in the first hours of treatment due to an incorrect diagnosis
 - ⇒ pain onset
 - pain in aortic dissection is abrupt in onset and maximal at the time of onset.
 - pain associated with **MI** starts slowly and gains in intensity with time.
 - ⇒ Pain character
 - In dissection although tearing is the classical description, the pain is described as sharp more often than tearing, ripping, or stabbing.
 - In MI it is usually more oppressive and dull.
 - ⇒ Pain site
 - with distal dissections the pain location is between the scapulae and in the back.
- Oesophageal rupture
 - ⇒ Features that favor oesophageal rupture over aortic dissection include:
 - The history of onset while eating
 - Blood pressure equal in both arms
 - No diastolic murmur
 - Good peripheral pulses, and
 - Presence of a pleural effusion.

the history of chest pain <u>radiating to the back</u> is concerning., <u>early diastolic murmur</u> suggesting aortic valve regurgitation, <u>ECG changes in the inferior territory</u> and indicating occlusion of the right coronary artery. These features combined suggest that the <u>aortic dissection has tracked back to the heart</u> itself. The enlarged heart on chest X-ray may suggest a <u>haemopericardium</u>, and the patient should be assessed for <u>cardiac tamponade</u> given his <u>low blood pressure</u>. This patient is highly unstable and requires urgent cardiothoracic involvement. the most appropriate next step in the management \rightarrow Bedside echocardiogram and urgent cardiothoracic review

Management

- Type A
 - ⇒ surgical management, but blood pressure should be controlled to a target systolic of 100-120 mmHg whilst awaiting intervention
 - ⇒ The most appropriate management strategy is to provide adequate analgesia and urgently reduce the blood pressure with intravenous antihypertensives: beta-blockers first line, and then nitroprusside. Then the cardiothoracic surgeons should be contacted.
 - ⇒ perioperative management of patients undergoing high risk vascular surgery
 - prophylactic beta blockers for high risk vascular surgery (including those patients with COPD).
 - Bisoprolol is the best clinical choice
 - Atenolol is next best choice; it is cardioselective and long acting, reducing risk of postoperative myocardial ischaemia and tachycardia.
- Type B
 - ⇒ conservative management
 - bed rest
 - reduce blood pressure IV labetalol to prevent progression
 - ⇒ endovascular repair of type B aortic dissection may have a role in the future

Complication

- haemopericardium and cardiac tamponade
 - ⇒ If the dissection (involving the ascending aorta (Stanford type A) results in a tear of the tunica externa, aortic blood can leak into the pericardium.
 - Management of aortic dissection complicated by haemopericardium and cardiac tamponade
 - acute type A aortic dissection complicated by haemopericardium and cardiac tamponade:
 - ❖ Relatively stable patient → immediate surgical repair and surgical evacuation of haemopericardium.
 - Pericardiocentesis in these patients can increase the intra-aortic pressure and reopen the closed communication between false lumen and pericardium. This can lead to recurrent cardiac tamponade that may be lethal.
 - marked hypotension or electromechanical dissociation → pericardiocentesis

Prevention

- The management of patients with predisposing inherited diseases such as Marfan's syndrome and Ehlers-Danlos syndrome should include:
 - ⇒ Periodic aortic diameter screening.
 - ⇒ Lifelong beta-blockade.
 - ⇒ Consideration of prophylactic replacement of the aortic root if dilated.
 - ⇒ Moderate restriction of physical activity.

Prognosis

- Mortality for untreated aortic dissection is 25–30% at 24 h and 65–70% at 2 weeks
- dissections confined to the descending aorta are associated with better survival (80%).

Aortic aneurysms

Aortic aneurysms

- Most common cause of aneurysms → atherosclerosis
- The nice guidelines state that an aortic aneurysm of greater than 5.5 cm in diameter should be treated. Below this size, the risk of dissection is outweighed by the risk of surgery.

Definition

 Localized dilation of all three layers of the abdominal aortic wall (intima, media, and adventitia) to ≥ 3 cm

Epidemiology

• Sex: ♂ > ♀: ~ 2:1

Risk factors

- Advanced age
- Smoking (most important risk factor)
- Atherosclerosis
- Hypercholesterolemia and arterial hypertension
- Positive family history

Localization

- Infrarenal: below the renal arteries: Most common location
- Suprarenal: above the renal arteries

Features

- Aortic aneurysms are usually asymptomatic or have nonspecific symptoms.
- Lower back pain
- Pulsatile abdominal mass
- Bruit on auscultation

Abdominal vs. thoracic aortic aneurysm

Characteristics	Abdominal aortic aneurysm	Thoracic aortic aneurysm
Location	Below the renal arteries (most common)	Ascending aorta (most common)
Epidemiology	Advanced agePredominantly menMore common than TAA	Advanced agePredominantly men
Etiology	 Smoking (most important risk factor) Atherosclerosis Hypercholesterolemia and arterial hypertension 	 Arterial hypertension Bicuspid aortic valve Tertiary syphilis [10] Connective tissue diseases (e.g., Marfan syndrome, Ehlers-Danlos syndrome) Trauma Smoking
Clinical features	Pulsatile abdominal mass Bruit on auscultation Lower back pain	Feeling of pressure in the chest Thoracic back pain
Diagnostics	Abdominal ultrasound (best initial and confirmatory test)	Chest x-ray and CTA of chest
Therapy	 Indications for repair ⇒ Diameter: ≥ 5.5 cm ⇒ Expansion rate: ≥ 1 cm/year ⇒ Symptomatic aneurysm ⇒ Complications (e.g., rupture) 	Indications for repair Diameter: ascending aneurysm ≥ 5.5 cm; descending aneurysm ≥ 6.5 cm Expansion rate: ≥ 1 cm/year Symptomatic aneurysm Complications (e.g., rupture)

Aortic regurgitation (AR)

Turner's syndrome - most common cardiac defect is bicuspid aortic valve

Causes

- due to valve disease
 - ⇒ bicuspid aortic valve
 - the most common cause of chronic AR in a young patient is a congenital bicuspid valve.
 - Bicuspid valve is also a common cause of early-onset aortic stenosis.
 - ⇒ infective endocarditis
 - the vegetations prevent the valve from creating a proper seal to prevent backflow during diastole.
 - ⇒ rheumatic fever
 - ⇒ connective tissue diseases e.g. RA/SLE
- due to aortic root disease

- ⇒ aortic dissection
- ⇒ Spondyloarthropathies (e.g. ankylosing spondylitis)
 - Ankylosing spondylitis is strongly associated with aortic regurgitation (occurs in 4% of cases).
 - An aortitis leads to aortic root dilatation with subsequent failure of leaflet coaptation.
- ⇒ hypertension
- ⇒ syphilis
- ⇒ Marfan's,
- ⇒ Ehler-Danlos syndrome

Causes of acute aortic regurgitation:

- · ascending aortic dissection,
- infective endocarditis,
- · collagen vascular disorders such as Marfan's
- trauma.
- dehiscence of a prosthetic valve.

Features

- · early diastolic murmur
 - ⇒ heard along the left sternal border
 - ⇒ heard best while the patient is leaning forward on deep expiration.
- · collapsing pulse
- · wide pulse pressure
- · mid-diastolic Austin-Flint murmur
 - ⇒ It is a low frequency mid/late diastolic murmur
 - due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams.
 - There is no correlation between the presence of murmur and severity of AR, or aetiology.
- Note that there is often an <u>aortic systolic flow murmur</u> because there is an increased volume of blood in the LV due to the regurgitation.
- Isolated LV dilatation (other chambers are normal) on ECHO due to volume overload
 - ⇒ (AS, HOCM & ↑ BP → hypertrophy and a smaller LV cavity)
- Pulsus bisferiens; increased pulse pressure; visible, forceful, and bounding peripheral pulses (water hammer)
- Corrigan's pulse visible and vigorous arterial pulsations in neck
- Musset's sign Bobbing of the head, due to the arterial pulsations in the neck
- · Quincke's sign Capillary pulsations of the nail bed
- Muller's sign Pulsations of the uvula
- Traube's sign Loud systolic sound over femoral arteries ('pistol-shot' femorals)
- Duroziez sign diastolic murmur proximal to femoral artery compression (due to flow reversal).
- Hill's sign (Higher systolic in leg than arm)

Signs of severity of AR

- Soft S2
- S3
- Austin Flint murmur (functional mdm at the apex due to regurgitant jet striking the anterior leaflet of the MV, therefore obstructing flow from the LA into the LV)
- characteristic of the murmur. (Duration and loudness) (cf with AS)
 - ⇒ As the lesion becomes **more severe**, the <u>murmur shortens</u>.
- · Apex beat displaced and thrusting

- CCF (pulmonary oedema)
- Wide pulse pressure
- · collapsing pulse,
- Hill's sign (Higher systolic in leg than arm)

Investigations

- Echocardiogram (the most important test)
 - ⇒ Echocardiographic markers of severe AR
 - Width of AR jet on colour flow > 65 % of LVOT
 - regurgitant fraction (RF) > 50 %
 - left ventricular end-diastolic diameter (LVEDD) > 70mm
 - left ventricular end-systolic diameter (LVESD) > 50mm
- · Cardiac catheterisation
 - ⇒ may be performed if there is doubt over the severity of the regurgitation;
 - ⇒ severity is estimated by the degree of contrast that fills the ventricles after injection into the aortic root.

Treatment

- Asymptomatic:
 - ⇒ Asymptomatic without signs of sever AR:
 - ACEI improve the prognosis in asymptomatic left ventricular dysfunction.
 - Beta blockers <u>should be avoided</u> as these prolong diastole and therefore would increase the regurgitant fraction.
 - Asymptomatic with signs of sever AR: surgery (Indications for surgery in asymptomatic):
 - signs of sever AR (echo criteria):
 - **❖ LV ejection fraction under 50%**
 - LV end diastolic diameter greater than 7 cm
 - LV end systolic diameter greater than 5 cm.
 - ⇒ Patient has moderate AR and is undergoing coronary artery bypass surgery or other surgery involving the ascending aorta = surgery
- Symptomatic: Surgical
 - ⇒ Symptomatic (CCF, angina)
 - ⇒ deteriorating exercise tolerance, or
 - ⇒ abnormal hemodynamic responses to exercise, such as inability to augment blood pressure during a treadmill study

Aortic stenosis (AS)

Aortic stenosis - most common cause:

- younger patients < 65 years: bicuspid aortic valve
- older patients > 65 years: calcification

Aortic stenosis - S4 is a marker of severity

Angiodysplasia is associated with aortic stenosis

Epidemiology

Aortic stenosis (AS) is the most common valve problem in the United Kingdom.

Risk factors

- age >60 years
- · congenitally bicuspid aortic valve
- · rheumatic heart disease
- chronic kidney disease

Causes

- degenerative calcification (tricuspid aortic valve calcification)
 - ⇒ most common cause in older patients > 65 years
- congenital bicuspid aortic valve (BAV)
 - ⇒ most common cause in younger patients < 65 years
 - ⇒ BAV is the most common form of congenital heart disease in adults (1-2% of population).
 - ⇒ The European Society of Cardiology states that there is an estimated 10% chance of a first degree relative being affected, which increases to 20-30% if you consider aortopathy. NOTCH1 gene mutations may be responsible.
 - It is possible that up to a third of relatives of patients with a bicuspid valve have valve or aortic abnormalities (often a dilated aorta).
 - NOTCH1 gene mutations may be responsible.
 - most helpful in establishing a diagnosis of congenital bicuspid valve as the aetiology is → Systolic ejection click (best heard at the apex)
 - ⇒ aortic valve replacement is eventually likely to be required
 - Only 15% of patients with a bicuspid aortic valve will have a normally functioning valve in the fifth decade, and this often continues to deteriorate with age.
- William's syndrome (supravalvular aortic stenosis)
- post-rheumatic disease → fibrosis → Commissural fusion on ECHO
- subvalvular: HOCM

Pathophysiology

- Pathophysiological response in aortic stenosis
 - ⇒ The LV hypertrophies increase (in the size of myocytes) in a concentric rather than an eccentric (asymmetric) - manner in response to the increase in afterload.

⇒ There is also an increase in interstitial collagen and little fibrosis

The triad of angina, left ventricular failure and syncope is classical to aortic stenosis.

Features

Narrow pulse pressure and new murmur → aortic stenosis

- Symptoms
 - ⇒ heart failure
 - ⇒ SAD
 - Syncope (40%)
 - Angina or chest pain (50%)
 - Dyspnea (60%)
 - Exertional dyspnea is the most common initial complaint
- Physical exam
 - ⇒ pulse
 - narrow pulse pressure
 - slow rising pulse
 - pulsus parvus et tardus
 - weak pulses with a delayed peak
 - ⇒ Displaced apex beat
 - ⇒ thrill
 - ⇒ ejection systolic murmur (ESM)
 - crescendo-decrescendo murmur
 - typically, a mid-systolic ejection murmur
 - heard best with the diaphragm of the stethoscope in the 2nd intercostal space in a patient who is sitting upright leaning forward.
 - in the elderly the more high frequency components of aortic stenosis may be <u>heard best at the apex</u>, the so called (<u>Gallavardin</u> phenomenon)
 - may have ejection click
 - radiates to carotid arteries (left often louder than right). radiate to the right neck
 - decreases with standing, Valsalva, or handgrip
 - increases with amyl nitrate, squat, or leg raise
 - The <u>intensity</u> of the systolic murmur <u>does not</u> correspond to the severity of aortic stenosis:
 - As LV contractility decreases in critical AS, the murmur becomes softer and shorter. The intensity of the murmur may therefore be misleading in these circumstances.
 - the <u>timing of the peak</u> and the <u>duration</u> of the murmur correspond to the severity of aortic stenosis.
 - The more severe the stenosis, the longer the duration of the murmur and the more likely it peaks at late systole.
 - ⇒ S4 heart sound
 - from stiff or hypertrophic ventricle
 - ⇒ S2 (Character of S2)
 - soft/absent S2
 - paradoxical splitting of S2
 - heard on expiration rather than inspiration

Associated conditions

- · hemolytic anemia
- predisposes to bleeding due to an <u>acquired von Willebrand deficiency</u> caused by <u>turbulent</u> flow across the stenotic valve.
- · chronic gastrointestinal bleeding that is associated with angiodysplasia.

Severity of aortic stenosis

Features of severe aortic stenosis

- 1. narrow pulse pressure
- 2. slow rising pulse
- 3. delayed ESM
- 4. soft/absent S2
- 5. **S**4
- 6. thrill
- 7. duration of murmur
- 8. left ventricular hypertrophy or failure
- The severity of (AS) can be accurately assessed with echocardiography.
- the severity of AS is difficult to assess with echocardiography when cardiac output is low.
- Catheterization to determine the severity of AS is reserved for patients in whom echocardiography is nondiagnostic
- The volume of the murmur has **NO** relationship to the severity of the stenosis

In a patient with aortic stenosis, what will lead to an overestimation of the severity of the problem when assessed by echocardiography?

- Aortic regurgitation
 - due to large volumes of blood passing over the valve at high velocities

Which condition is most associated with quietening of the aortic stenotic murmur?

- ⇒ Left ventricular systolic dysfunction → decreased flow-rate across the aortic valve and hence a quieter murmur.
- Atrial fibrillation
 - Where the R-R interval is particularly short, such as in atrial fibrillation, flow across
 the valve is reduced, as such the intensity of the murmur is variable and may be
 significantly reduced.
 - Aortic regurgitation has no effect on the intensity of the murmur, such that in patients with mixed aortic valve disease, the stenotic murmur is still clearly audible.

Conditions which leads to accentuation of the murmur → increased flow across the murmur.

- · High output cardiac failure
- severe thyrotoxicosis

The predominant component of mixed aortic valve disease is determined by the murmur that is louder (ejection systolic murmur in aortic stenosis and mid diastolic murmur for aortic regurgitation).

Evaluation

- Severe AS is defined by a valve area of less than 1.0 cm².
- distinguish patients with true severe (AS) with secondary LV dysfunction from those who have a falsely low calculated aortic valve area because of low cardiac output.

- ⇒ calculated valve area in patients with severe left ventricular (LV) dysfunction can be falsely low because low cardiac output reduces the valve opening forces.
- ⇒ It is important to distinguish patients with true severe (AS) with secondary LV dysfunction from those who have a falsely low calculated aortic valve area because of low cardiac output.
- An important method of distinguishing between the two conditions is to assess the haemodynamics after increasing the cardiac output by dobutamine infusion during echocardiography or cardiac catheterisation.
 - Patients with truly severe AS manifest an increase in trans-aortic pressure gradient while the valve surface area remains the same during dobutamine infusion;
 - those with falsely low calculated valve area manifest an increase in calculated valve surface area.
- ⇒ Dobutamine echocardiography is also important to assess LV contractile reserve.
 - Patients who have 20% or more increase in stroke volume after dobutamine infusion have a much better prognosis after surgery compared to those who do not have LV contractile reserve.

What is the difference between aortic stenosis and aortic sclerosis?

- Both aortic stenosis and aortic sclerosis are :
 - ⇒ senile degeneration of the valve
 - ⇒ there is an ejection systolic murmur,
- Unlike aortic stenosis, aortic sclerosis have:
 - ⇒ Occur in > 25% of > 65 year of age
 - Aortic stenosis occur in > 2% of > 65 year of age
 - ⇒ Absence of stenosis
 - no carotid radiation.
 - normal pulse (character and volume)
 - normal S2.

Investigations

- Echocardiography
 - ⇒ transthoracic echocardiogram (TTE) initially
 - ⇒ transesophageal echocardiogram (TEE) is more accurate
 - Although echocardiography will aid in diagnosis, gradient across the aortic valve may be underestimated because of the possibility of multiple echo signals and coexistent left ventricular dysfunction.
- Left heart catheterization
 - ⇒ most accurate diagnostic test (the definitive investigation of choice)
 - ⇒ to assess pressure gradient across the valve
 - ⇒ only indicated to confirm the diagnosis if echocardiography is unclear
 - ⇒ findings
 - elevated pressure gradient (> 30 mmHg)
 - In the context of poor LV function, the aortic valve gradient may be normal or only mildly raised in the presence of a severely narrowed aortic valve area.
- The next step in management after diagnosis → Coronary angiography
 - ⇒ Coronary artery disease (CAD) is common in patients with AS
 - ⇒ Progressing straight to aortic valve replacement is not advised; significant coronary artery disease should be ruled out first, as CABG may be required at the same time as valve replacement.

Patients undergoing open surgical valve replacement should first undergo coronary angiography to exclude any coronary stenosis that could simultaneously be treated with bypass grafting.

Management

Aortic stenosis management: AVR if symptomatic, otherwise cut-off is gradient of 50 mmHg

- if asymptomatic then observe the patient is general rule
- if symptomatic then valve replacement
 - ⇒ The patient's symptomatology is the most important determinant in terms of the decision to operate

There are three important factors to consider regarding management of aortic stenosis:

- 1. Presence of symptoms
- 2. The gradient across the valve on echocardiogram
- 3. Evidence of left ventricular dysfunction.
- Symptomatic patient
 - ⇒ Fit for surgery → aortic valve replacement
 - the best treatment option in an older person who can undergo the surgery.
 - ⇒ Not fit for aortic valve replacement
 - Transcatheter aortic valve implantation (TAVI)
 - The catheter-delivered device produces similar one-year survival as aortic valve replacement but a higher risk of stroke, TIAs and vascular complications.
 - Balloon valvuloplasty
 - Balloon aortic valvuloplasty is a palliative procedure prone to restenosis for patients unsuitable for other interventions.
- Asymptomatic patient
 - ⇒ with <u>severe stenosis</u> (transvalvular gradient > 50 mmHg, valve area <1 cm²) but has an ejection fraction of less than 50%.
 - should be referred for aortic valve replacement or TAVI if unsuitable.
 - ⇒ with severe stenosis but has an ejection fraction is greater than 50%.
 - Exercise testing would be recommended
 - ❖ If pass exercise testing, then → reviewed in six months.
 - ⇒ echo follow-up
 - asymptomatic with mild stenosis → every 3 to 5 years
 - asymptomatic with moderate stenosis → every 1 to 2 years
 - asymptomatic with severe stenosis → every 6 to 12 months.

Indicator of poor prognosis

- Clinical features of left ventricular failure
 - ⇒ deteriorating LV function (ejection fraction less than 40%)
- Symptomatology
 - ⇒ exertional breathlessness or presyncope/syncope
- Increasing gradient across the valve (above 70 mmHg)
- Age of patient

Heyde's syndrome

- association between microcytic anaemia and calcific aortic stenosis.
- Heyde syndrome refers to a <u>triad of</u>
 - 1. aortic stenosis,
 - 2. acquired coagulopathy (von Willebrand syndrome type 2A) and
 - **3.** anaemia due to bleeding from intestinal angiodysplasia or from an idiopathic site.
 - Angiodysplasia most commonly occur in the ascending colon, particularly the caecum.
- Pathophysiology
 - ⇒ destruction of von Willebrand's factor as the platelets traverse the stenosed valve resulting in bleeding per rectum.
- Investigation
 - ⇒ The investigation of choice after valve replacement is mesenteric angiography as the bleeding vessels are poorly visualised on colonoscopy.
 - This would look for the presence of angiodysplasia, which may be associated with aortic stenosis.
 - ⇒ All patients with aortic stenosis should be screened for iron deficiency anaemia.
- Treatment
 - ⇒ replace the valve
 - ⇒ Resection of the diseased bowel has also been described as a treatment.
- There is an association with jaundice and aortic stenosis; this is thought to be due to microangiopathic haemolysis.

Williams syndrome

<u>Supravalvular aortic stenosis</u> is the congenital cardiovascular deformity most often associated with Williams syndrome.

- Supra-valvar AS is one of the characteristic findings of Williams syndrome along with:
 - ⇒ unusual elfin facies,
 - excellent verbal skills contrasted with intellectual disability and lack of social <u>inhibition</u>.
 - ⇒ hypercalcemia (due to increased sensitivity to vitamin D.)
- caused by a microdeletion of the elastin gene on long arm of chromosome 7

Coarctation of the aorta

Definition:

 congenital narrowing of the descending aorta, most commonly at the site of insertion of the ductus arteriosus

Overview

- more common in males (despite association with Turner's syndrome)
- a bicuspid valve is found in approximately 50% of patients with coarctation of the aorta.
- site of coarctation:
 - distal to the origin of the left subclavian artery
 - The commonest site
 - The systolic BP in the arms exceeds that in the leg.
 - ⇒ **proximal** to the origin of the left subclavian artery

- occurs in 15% of cases of coarctation
- if the systolic BP in the right arm is higher than that of the left arm by more than 30 mmHg, the left subclavian is involved in the coarctation (ie coarctation is proximal to the origin of the subclavian)

Features

- · Most patients are asymptomatic
- infancy: heart failure
- · claudication of the calf muscles.
 - pain in calves is almost certainly due to poor distal blood supply.
- Hypertension
 - ⇒ the **most common** presenting feature in adults
- headache and nose bleeds occur due to hypertension proximal to the coarctation,
- differential blood pressures between the right and left arms
- radio-femoral delay
- mid systolic murmur, and thrill
 - ⇒ maximal over back.
 - ⇒ continuous murmur over the thoracic spine usually originates from small, tight coarctation (< 2 mm).
- · apical click from the aortic valve

Complications

- · Secondary hypertension
- development of cerebral aneurysms
 - ⇒ may present with intracranial haemorrhage from a ruptured berry aneurysm
- Left ventricular failure.
- · Bacterial endocarditis.

Associations

- Bicuspid aortic valve
 - ⇒ the commonest associated congenital abnormality
 - ⇒ occurs in 50% of the coarctations.
- patent ductus arteriosus (PDA)
- Turner's syndrome
 - ⇒ Female patients diagnosed with coarctation of the aorta should have a **karyotype analysis** to rule out <u>Turner syndrome</u>.
- berry aneurysms
- · neurofibromatosis

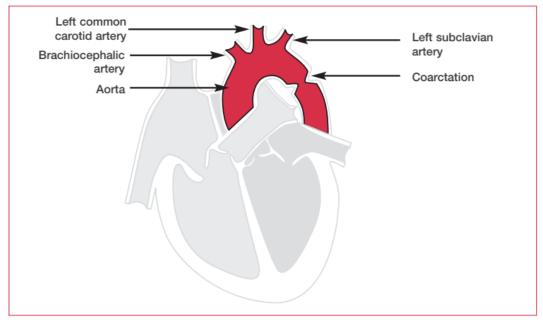
Investigations

- Radiograph
 - □ Cardiomegaly
 - ⇒ ↑ pulmonary vascular markings
 - ⇒ rib notching
 - notching of the inferior border of the ribs (due to collateral vessels)
 - usually manifests in adults and older children, as it takes time to develop.
 - ⇒ may demonstrate an indentation of the aortic shadow at the site of the coarctation.
 - ⇒ rib notching is not seen in young children
- Echocardiography with doppler (confirmatory test):
 - ⇒ location and extent of stenosis:
 - ⇒ concurrent anomalies

Treatment

- · Balloon angioplasty and stenting is
 - ⇒ the preferred intervention in adults.
 - ⇒ surgical correction is indicated if the pressure gradient across the coarctation is above 20 mmHq, even without associated hypertension.

Prostaglandin E1 should be administered to neonates with aortic coarctation to keep the ductus arteriosus open.



Coarctation of the aorta.

Differences in blood pressure between arms:

- up to 10 mmHg difference → Normal variant (physiological)
- difference of greater than 10 mmHg: → abnormal:
 - ⇒ + radio-radial or radio-femoral delay (NO Leg claudication) → proximal **coarctation** of the aorta (involves the left subclavian artery origin)
 - ⇒ + arm claudication, intermittent vertigo, ataxia or diplopia, or facial sensory symptoms (NO Leg claudication) → Subclavian steal syndrome
 - ⇒ + Leg claudication (chronic intermittent leg pain, exacerbated by exercise and relieved by rest) → Peripheral vascular disease

Bicuspid aortic valve

Overview

- occurs in 1-2% of the population
- Bicuspid aortic valve tends to be sporadic although there is a reported familial incidence of approximately 9%.
- usually asymptomatic in childhood
 the majority eventually develop ass the majority eventually develop aortic stenosis or regurgitation

associated with:

- left dominant coronary circulation (the posterior descending artery arises from the circumflex instead of the right coronary artery)
- Turner's syndrome
- coarctation of the aorta (around 5% of patients)

Complications

- aortic stenosis/regurgitation as above
- higher risk for aortic dissection and aneurysm formation of the ascending aorta

Tricuspid regurgitation

Signs

- pan-systolic murmur
- giant V waves in JVP
- pulsatile hepatomegaly
- left parasternal heave

Causes

- pulmonary hypertension e.g. COPD (The most common cause)
- · right ventricular dilation
- · rheumatic heart disease
- infective endocarditis (especially intravenous drug users)
- · Ebstein's anomaly
- · carcinoid syndrome

Prosthetic valves

Prosthetic heart valves - mechanical valves last longer and tend to be given to younger patients

Prosthetic heart valves - antithrombotic therapy:

- · bioprosthetic: aspirin
- · mechanical: warfarin + aspirin

Mechanical valves - target INR:

aortic: 2.0-3.0mitral: 2.5-3.5

- The most common valves which need replacing are the aortic and mitral valve.
- There are two main options for replacement: biological (bioprosthetic) or mechanical.

Biological (bioprosthetic) valves	Mechanical valves
Usually bovine or porcine in origin	The most common type now implanted is the bileaflet valve. Ball-and-cage valves are rarely used nowadays
Advantages: not requiring Long-term anticoagulation Warfarin may be given for the first 3 months depending on patient factors. Low-dose aspirin is given long-term.	Advantages : have a low failure rate
Disadvantages calcification over time. must be replaced within 5 to 10 years. Most older patients (> 65 years for aortic valves and > 70 years for mitral valves) receive a bioprosthetic valve	Disadvantages ↑ risk of thrombosis meaning long-term anticoagulation is needed. Aspirin is normally given in addition unless there is a contraindication. Target INR • aortic: 2.0-3.0 • mitral: 2.5-3.5

Following the 2008 NICE guidelines for prophylaxis of endocarditis → antibiotics are no longer recommended for common procedures such as dental work.

Which pathological findings in the bioprosthesis has most likely led to the need for replacement?

⇒ Calcification with stenosis

<u>Supraventricular tachycardia (SVT)</u>

Definition

The term 'SVT' literally indicates tachycardia [atrial rates >100 beats per minute at rest, the
mechanism of which involves tissue from the His bundle or above. Traditionally, SVT has
been used to describe all kinds of tachycardias apart from ventricular tachycardias (VTs)
and AF.

Causes

- Atrioventricular nodal re-entry tachycardia (AVNRT).
 - ⇒ the most common supraventricular tachycardia,
 - ⇒ twice as common in females as in males
 - ⇒ the incidence is 1–3 per 1000
 - ⇒ Small elevations in troponin are occasionally seen in this situation, but there are no ECG changes to suggest a myocardial infarction.
- Atrioventricular re-entry tachycardias (AVRT)
- Junctional tachycardias.

Differential diagnosis

Paroxysmal SVT ⇒ would start and stop suddenly, **not gradually.**Panic attacks ⇒ breathlessness and palpitations start and stop **gradually.**

Management

Vagal manoeuvres and adenosine are the treatments of choice for the acute therapy of SVT, and may also provide important diagnostic information.

Acute management

- ⇒ haemodynamically stable patient:
 - 1st line : vagal manoeuvres : e.g. Valsalva manoeuvre
 - Carotid sinus massage is contraindicated in patients with <u>carotid</u> vascular disease
 - 2^{nd} line: intravenous adenosine $6mg \rightarrow 12mg \rightarrow 12mg$
 - Adenosine can cause flushing, chest pain, and dizziness.
 - contraindicated in asthmatics verapamil is a preferable option
 - 3rd line: Verapamil or diltiazem i.v. or Beta-blockers (i.v. esmolol or metoprolol) should be considered if vagal manoeuvres and adenosine fail.
 - 4th line: Synchronized DC cardioversion
- ⇒ haemodynamically unstable patient:
 - Synchronized DC cardioversion: start with 70-120 J biphasic (100 J monophasic).
- · Prevention of episodes
 - ⇒ 1st line: beta-blockers or
 - ⇒ 2nd line: radio-frequency ablation
- Do not use flecainide or propafenone in patients with LBBB, or ischaemic or structural heart disease.
- Verapamil is not recommended in wide QRS-complex tachycardia of unknown aetiology.
- Flecainide and propafenone are not recommended as first-line antiarrhythmic drugs in patients with ventricular dysfunction and severe fibrosis.

SVT in pregnancy

- Tachyarrhythmias may increase during pregnancy although the causes are not entirely clear.
- Termination of acute SVT:
 - ⇒ haemodynamic stable:
 - Vagal manoeuvres and, if these fail, adenosine (adenosine appears to be safe in pregnancy).
 - An i.v. beta-1 selective blocker (except atenolol) should be considered for acute conversion or rate control of SVT.

- Prevention of recurrent SVT
 - ⇒ in patients without WPW syndrome :
 - If possible, avoid all antiarrhythmic drugs during the first trimester of pregnancy.
 - 1st line: beta-1 selective agents (but not atenolol) beta-blockers.
 - The cardio-selective beta-1-blockers include atenolol, betaxolol, bisoprolol, esmolol, acebutolol, metoprolol, and nebivolol.
 - Metoprolol is the preferred and safest Beta-blocker in prophylaxis for SVT in pregnancy (it is a short acting β blocker and a TDS regimen is required).
 - 2nd line: verapamil
 - 3rd line: Fluoroless catheter ablation
 - ⇒ Prevention of recurrent SVT in patients with WPW syndrome :
 - 1st line : Flecainide or propafenone
 - 2nd line: Fluoroless catheter ablation

Sinus arrhythmia

- The (ECG) shows normal P wave, PR interval, QRS complex and each P wave conducted to ventricles.
- There is a gradual decrease in R–R interval and then an increase again. This slight beat-to-beat variation (rhythmic and cyclical variation) is termed as sinus arrhythmia.
- the most common cause is respiration.
 - ⇒ Respiratory sinus arrhythmia is thus heart rate variability in synchrony with respiration, and is normal in children and young adults.
 - ⇒ The R–R interval decreases with inspiration and increases with expiration.
- Anxiety → reassured.



Premature ventricular ectopic (PVEs)

The first line management of supraventricular ectopics is generally reassurance and lifestyle modifications (eg: reduce alcohol and caffeine intake). If symptoms persisted, then a beta blocker would be first line.

- usually seen in normal hearts;
- palpitations are described as an early beat with a pause followed by an unusually strong or 'pounding' beat, or simply as a 'flip-flop';
 - ⇒ Symptoms are usually worse at rest and may disappear with exercise.
 - Symptoms which increase on exercise are more worrying and significant.
- may be associated with caffeine intake
- Investigations
 - ⇒ baseline ECG without symptoms: typically normal
 - ⇒ ambulatory ECG: isolated wide QRS complexes
 - If symptoms are short-lived but frequent (>2-3 times per week), use a 24-hour Holter monitor
 - If symptoms are short-lived and infrequent (<1 per week), use an event monitor or transtelephonic recorder
 - ⇒ Exercise stress testing
 - the relation of extrasystoles to exercise may have prognostic importance.
 - ⇒ Echocardiography to assess LV function and heart structure.
- For PVE to be **significant** they have to meet the following criteria:
 - ⇒ Occurring frequently (6 or more beats/min)
 - ⇒ PVE in bigeminal rhythm
 - ⇒ PVE in short runs of ventricular tachycardia
 - ⇒ PVE exhibiting R-on-T phenomenon
 - ⇒ PVE associated with serious organic heart disease and left ventricular decompensation.
- Treatment
 - ⇒ Not significant PVE → Reassurance
 - ⇒ Significant PVE
 - beta-blockers
 - Radiofrequency catheter ablation of the ectopic focus
 - Curative with good outcome

Ventricular extrasystoles are the most common type of arrhythmia that occurs after myocardial infarction.

Management of symptomatic atrial extrasystoles

- beta-blockers (atenolol or metoprolol).
- Atrial extrasystoles arising from the pulmonary veins may be treatable by the procedure of pulmonary vein isolation.

Arrhythmogenic right ventricular cardiomyopathy(ARVC)

Overview

- Arrhythmogenic right ventricular cardiomyopathy (ARVC, also known as arrhythmogenic right ventricular dysplasia or ARVD) is a form of inherited cardiovascular disease which may present with syncope or sudden cardiac death.
- It is generally regarded as the second most common cause of sudden cardiac death in the young after hypertrophic cardiomyopathy.
- Although ARVC was initially described in the right ventricle, most patients have biventricular involvement.

Pathophysiology

- inherited in an autosomal dominant pattern with variable expression
- the right ventricular myocardium is replaced by fatty and fibrofatty tissue
- around 50% of patients have a mutation of one of the several genes which encode components of desmosome

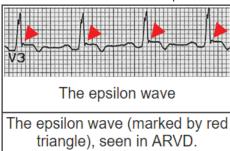
Presentation

- palpitations
- syncope
- sudden cardiac death

Investigation

epsilon potential is seen on the ECG of patients with -> Right ventricular dysplasia

- ECG abnormalities in V1-3:
 - ⇒ Typically, T wave inversion.
 - ⇒ An **epsilon wave** is found in about 50% of those with ARV this is best described as a terminal notch in the QRS complex



- echo changes are often subtle in the early stages but may show an enlarged, hypokinetic right ventricle with a thin free wall
- magnetic resonance imaging is useful to show fibrofatty tissue

Management

- drugs: sotalol is the most widely used antiarrhythmic
- · catheter ablation to prevent ventricular tachycardia
- · implantable cardioverter-defibrillator

Naxos disease

- an autosomal recessive variant of ARVC
- a triad of ARVC, palmoplantar keratosis, and woolly hair

Atrial fibrillation (AF) (NICE guideline April 2021)

Overview

- AF is the most commonly encountered cardiac arrhythmia.
- Hypertension is the most common risk factor for AF.
- In 15% of cases, AF is idiopathic
- AF most commonly originates from the <u>roots of the pulmonary veins</u>. (longitudinal smooth muscle fibers in the pulmonary vein)

classification

Definition	Duration of atrial fibrillation	
Paroxysmal	Up to 7 days	
Persistent	Longer than 7 days	
Permanent	Cardioversion failed or not attempted	

Classification of atrial fibrillation.

Classification of atrial fibrillation (AF): AF classified into 3 patterns:

- 1. **first detected episode** (irrespective of whether it is symptomatic or self-terminating)
- 2. recurrent episodes, when a patient has 2 or more episodes of AF:
 - paroxysmal AF:
 - episodes of AF terminate spontaneously.
 - episodes last less than 7 days (typically < 24 hours).</p>
 - persistent AF
 - the arrhythmia is not self-terminating.
 - episodes usually last greater than 7 days
- 3. permanent AF
 - there is continuous atrial fibrillation which cannot be cardioverted or if attempts to do so are deemed inappropriate.
 - Treatment goals are therefore rate control and anticoagulation if appropriate

Symptoms and signs

- Symptoms
 - ⇒ Palpitations
 - ⇒ Dyspnea
 - ⇒ chest pain
- Signs
 - ⇒ irregularly irregular pulse

Complications

 AF is poorly tolerated in elderly and often leads to pulmonary oedema even in the presence of a relatively normal left ventricle (LV).

Diagnosis

- if an irregular pulse is detected ⇒ Perform a 12-lead electrocardiogram (ECG)
- In people with suspected paroxysmal AF undetected by ECG:
 - ⇒ if asymptomatic episodes are suspected or symptomatic episodes are less than 24 hours apart ⇒ use a 24- hour ambulatory ECG monitor
 - ⇒ if symptomatic episodes are more than 24 hours ⇒ use an ambulatory ECG monitor, event recorder or other ECG technology.

Assessment

- Assessment of stroke and bleeding risks
 - ⇒ Assess stroke risk by using the CHA2DS2-VASc score
 - ⇒ Assess the bleeding risk when considering starting anticoagulation by using the ORBIT bleeding risk score
 - ⇒ modify risk factors for bleeding:
 - uncontrolled hypertension
 - poor control of international normalised ratio (INR) in patients on vitamin K antagonists
 - concurrent medication, including antiplatelets, selective serotonin reuptake inhibitors (SSRIs) and non- steroidal anti- inflammatory drugs (NSAIDs)
 - harmful alcohol consumption
 - reversible causes of anaemia.
- Assessment of cardiac function by transthoracic echocardiography (TTE) as a baseline and to look for underlying structural or functional heart disease.

Management

- Anticoagulation for stroke prevention
 - ⇒ 1st line: direct-acting oral anticoagulant (e.g. Apixaban, dabigatran, edoxaban, rivaroxaban), if CHA₂DS₂-VASc score ≥ 1 for men or ≥ 2 for women.
 - ⇒ 2nd line: If DOAC are contraindicated or not tolerated ⇒ vitamin K antagonist.
 - ⇒ 3rd line: If anticoagulation is contraindicated or not tolerated ⇒ consider left atrial appendage occlusion (LAAO).
- Rate and rhythm control
 - ⇒ Rate control:
 - the first-line treatment for AF **except** in:
 - 1) AF due to reversible cause
 - 2) heart failure caused by AF
 - 3) new-onset AF
 - atrial flutter which considered suitable for an ablation strategy to restore sinus rhythm
 - 5) if rhythm- control strategy would be more suitable based on clinical judgement.
 - Use beta-blocker (other than sotalol) or a rate-limiting calcium-channel blocker (diltiazem or verapamil)
 - Consider digoxin monotherapy for initial rate control if the person does no or very little physical exercise or other rate-limiting drug options are ruled out because of comorbidities.

⇒ Rhythm control:

- Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischaemic or structural heart disease.
- If drug treatment for long-term rhythm control after successful cardioversion is needed:
 - ❖ 1st line: beta-blocker
 - ❖ 2nd line: dronedarone
- Amiodarone for people with left ventricular impairment or heart failure.
- In people with infrequent paroxysms and few symptoms, or if symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy (in which antiarrhythmic drugs are taken only when an episode starts) should be considered
- a 'pill-in-the-pocket' strategy: In people with paroxysmal AF if:

- infrequent symptomatic episodes + no left ventricular dysfunction, or valvular or ischaemic heart disease + systolic BP >100 mmHg and a resting heart rate > 70 bpm + able to understand how to, and when to take the medication.
- try to get the patient back into, and maintain, normal sinus rhythm. This is termed cardioversion.
- Drugs (pharmacological cardioversion) and synchronised DC electrical shocks (electrical cardioversion) may be used for this purpose
- indications of Rhythm control :
 - coexistent heart failure,
 - first onset AF or
 - where there is an obvious reversible cause.

Do not use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent AF.

Rhythm control has no survival benefit over a rate control strategy

Reducing stroke risk → Anticoagulation

Young man with AF, no TIA or risk factors, no treatment is now preferred to aspirin (NO treatment)

Do not use antiplatelet therapy for stroke prevention in AF

- Some patients with AF are at a very low risk of stroke whilst others are at a very significant risk.
- NICE in 2014 suggest using the CHA₂DS₂-VASc score to determine the most appropriate anticoagulation strategy

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	Risk factor	Points
С	Congestive heart failure	1
Н	Hypertension (or treated hypertension)	1
A ₂	Age ≥ 75 years	2
	Age 65-74 years	1
D	Diabetes	1
S ₂	Prior Stroke or TIA	2
V	Vascular disease (including ischaemic heart disease and peripheral arterial disease)	1
s	Sex (female)	1

The table below shows a suggested anticoagulation strategy based on the score:

Score	Anticoagulation
0	No treatment
1	Males: Consider anticoagulation Females: No treatment (this is because their score of 1 is only reached due to their gender)
2 or more	Offer anticoagulation

Atrail fibrilation related to mitral stenosis

- atrial fibrillation related to valvular heart disease → Warfarin
 - ⇒ In patients with **non-valvular atrial fibrillation**, **novel oral anticoagulants** have the same efficacy as warfarin in preventing stroke.
- NICE guidelines suggest that valvular disease have high risk for thromboembolic events, and would benefit from anticoagulation.
- Mitral stenosis patients were excluded from the studies developing the CHADS-VASC score.
- None of the 'novel' anticoagulants currently available (rivaroxaban, apixaban, dabigatran) are indicated or licensed for atrial fibrillation related to valvular heart disease.

CHADS2-VASc scoring is generally used as a tool to assess need to anticoagulate a patient with AF. However, the following are **conditions that, if present, may trump the decision to anticoagulate:**

- 1. valvular heart disease
- 2. prior peripheral embolism, and
- 3. intracardiac thrombus.

Bleeding risk assessment (using the HASBLED scoring system)

- NICE recommend that we offer patients a choice of anticoagulation, including warfarin and the novel oral anticoagulants (NOACs).
- · Aspirin is no longer recommended for reducing stroke risk in patients with AF
- Doctors have always thought carefully about the risk/benefit profile of starting someone on warfarin.
- A history of falls, old age, alcohol excess and a history of previous bleeding are common things that make us consider whether warfarinisation is in the best interests of the patient.
- NICE now recommend we formalise this risk assessment using the HASBLED scoring system.

	Risk factor	Points
Н	Hypertension, uncontrolled, systolic BP > 160 mmHg	1
A	Abnormal renal function (dialysis or creatinine > 200) Or Abnormal liver function (cirrhosis, bilirubin > 2 times normal, ALT/AST/ALP > 3 times normal	1 for any renal abnormalities 1 for any liver abnormalities
s	Stroke, history of	1
В	Bleeding, history of bleeding or tendency to bleed	1
L	Labile INRs (unstable/high INRs, time in therapeutic range < 60%)	1
E	Elderly (> 65 years)	1
D	Drugs Predisposing to Bleeding (Antiplatelet agents, NSAIDs) Or Alcohol Use (>8 drinks/week)	1 for drugs 1 for alcohol

There are no formal rules on how we act on the HAS-BLED score although a score of >= 3
indicates a 'high risk' of bleeding, defined as intracranial haemorrhage, hospitalisation,
haemoglobin decrease >2 g/L, and/or transfusion.

Atrial fibrillation: cardioversion

Atrial fibrillation - cardioversion:

- if no structural heart disease → flecainide
- With structural heart disease → amiodarone

offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and start rate control if it is more than 48 hours or is uncertain

Cardioversion indications

- \Rightarrow Haemodynamically unstable patient \Rightarrow electrical cardioversion (DC cardioversion 200J \rightarrow 360J \rightarrow 360J)
 - Adverse signs necessitating DC cardioversion are:
 - ❖ Blood pressure (BP) ≤90 mmHg

- Chest pain
- Heart failure
- Impaired consciousness, and
- Heart rate ≥ 200 bpm.
- ⇒ Elective procedure where a rhythm control strategy is preferred → electrical or pharmacological cardioversion
 - Onset < 48 hours
 - Anticoagulation
 - ⇒ patients should be heparinised.
 - ⇒ Patients who have risk factors for ischaemic stroke should be put on lifelong oral anticoagulation.
 - Cardioversion method:
 - ⇒ electrical 'DC cardioversion'
 - ⇒ pharmacology:
 - amiodarone if structural heart disease,
 - flecainide or amiodarone in those without structural heart. disease
 - Post-cardioversion:
 - ⇒ further anticoagulation is unnecessary
 - Onset > 48 hours
 - prior to cardioversion:
 - ⇒ anticoagulation
 - for at least 3 weeks prior to cardioversion. OR
 - exclude a left atrial appendage (LAA) thrombus by transoesophageal echo (TOE). If excluded patients may be heparinised and cardioverted immediately.
 - ⇒ If there is a high risk of cardioversion failure (e.g. Previous failure or AF recurrence) then it is recommend to have at least 4 weeks amiodarone or sotalol prior to electrical cardioversion
 - ⇒ If the patient has a slow ventricular response of AF in the absence of anti-arrhythmic drugs, cardioversion should be performed after the insertion of a temporary transvenous-

pacing catheter

- Cardioversion method:
 - ⇒ NICE recommend electrical cardioversion, rather than pharmacological.
 - ⇒ The initial shock strength should be 100 J, followed by a second 200-J shock and a third 360-J shock
 - ⇒ If AF persists, a second 360-J shock with the paddles in the anteroposterior position can be attempted
- Post-cardioversion:
 - ⇒ Following electrical cardioversion patients should be anticoagulated for at least 4 weeks. After this time decisions about anticoagulation should be taken on an individual basis depending on the risk of recurrence
- Catheter AF ablation
 - Radiofrequency pulmonary vein isolation with ablation
 - the treatment of choice for patients who remain poorly controlled despite medical therapy,
 - in selected patients as first-line therapy for symptomatic paroxysmal AF
 - Anticoagulation for stroke prevention should be continued indefinitely in patients at high risk of stroke, even after apparently successful ablation of AF.

Surgical AF ablation

- Ablation can be performed in symptomatic patients during cardiac surgery for other reasons, or by stand-alone surgery either using open-chest techniques or by thoracoscopy.
- ⇒ Anticoagulation for stroke prevention should be continued indefinitely in patients at high risk of stroke, even after apparently successful ablation of AF.

The enlarged left atrial size suggests that a repeat DC cardioversion is unlikely to work for a sustained period.

H/O AF + enlarged left atrial size with previous DC cardioversions. the best long term treatment option → Refer for consideration of atrial fibrillation ablation → longer term good result.

AV node ablation:

- AV node ablation is reserved for those patients where pharmacological rate control is unsuccessful or not tolerated.
- The procedure is invasive and requires permanent pacemaker implantation.
- Patients who are candidates for this therapy include those with tachycardia induced cardiomyopathy despite pharmacologic efforts at rate control and intolerable symptoms despite aggressive attempts at pharmacologic therapy (in some cases, much of the symptom burden is due to medications rather than AF itself).

Do not perform cardioversion or catheter ablation without anticoagulation, unless an atrial thrombus has been ruled out by transoesophageal echocardiogram.

Amiodarone or vernakalant have been efficient in converting post-operative AF to sinus rhythm.

Vernakalant

- A Novel agent for the Termination of Atrial Fibrillation
- blocks sodium channels
- more prominent in vernakalant's mechanism of action is its ability to block certain potassium channels.
- Specifically, it blocks the atrial-selective potassium current, I_{Kur}, which is involved in atrial repolarization.

Atrial fibrillation: pharmacological cardioversion

Atrial fibrillation - cardioversion: amiodarone + flecainide

- . Agents with proven efficacy in the pharmacological cardioversion of atrial fibrillation
 - ⇒ amiodarone
 - ⇒ flecainide (if no structural heart disease)
 - with large doses of **oral agents** or with intravenous agents.
 - Large single doses of flecainide (300 mg) or propafenone (450-600 mg) given orally have been shown to convert patients to sinus rhythm.
 - Flecainide and propafenone are not used in people with :
 - known or suspected ischaemic heart disease.
 - individuals who are already on antiarrhythmic therapy.

- those with a prolonged QT interval because these agents may have pro-arrhythmic effects (torsade de pointes).
- ⇒ others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone
- · Less effective agents
 - ⇒ beta-blockers (including sotalol)
 - ⇒ calcium channel blockers
 - ⇒ digoxin

 - ⇒ procainamide

Atrial fibrillation: rate control and maintenance of sinus rhythm

Atrial fibrillation: rate control - beta blockers preferable to digoxin

The patient with very recent onset of atrial fibrillation is more likely to stay in sinus rhythm

- Agents used to control rate in patients with atrial fibrillation
 - ⇒ Beta-blockers
 - should be used first line for rate control.
 - cardioselective beta-blockers should be tried in patients with left ventricular systolic dysfunction even if they have a diagnosis of:
 - Chronic obstructive pulmonary disease (COPD)
 - Peripheral vascular disease
 - Diabetes
 - . Erectile dysfunction, or
 - Interstitial pulmonary disease.
 - Beta-blockers should not be commenced in the setting of acute exacerbations of COPD or cardiac failure
 - If one drug does not control the rate adequately NICE recommend combination therapy with diltiazem or digoxin
 - ⇒ calcium channel blockers (diltiazem)
 - ⇒ digoxin:
 - not considered first-line anymore as they are less effective at controlling the heart rate during exercise.
 - they are the preferred choice if the patient has coexistent **heart failure**
 - with borderline hypotension (eg: 95/70), COPD and AF, rate control
 without the possibility of worsening hypotension is the aim of
 intervention. Digoxin is therefore the optimal intervention. It will both slow
 the ventricular rate and support the blood pressure.
 - ⇒ If the duration of AF is unknown caution should be used when considering the use of drugs which may cardiovert the patient amiodarone and flecainide.
- Agents used to maintain sinus rhythm in patients with a history of atrial fibrillation
 - ⇒ sotalol
 - ⇒ amiodarone
 - ⇒ flecainide
 - ⇒ others (less commonly used in UK): disopyramide, dofetilide, procainamide, propafenone, quinidine
- The table below indicates some of the factors which may be considered when considering either a rate control or rhythm control strategy

Factors favouring rate control	Factors favouring rhythm control		
 Older than 65 years History of ischaemic heart disease 	 Younger than 65 years Symptomatic First presentation Lone AF or AF secondary to a corrected precipitant (e.g. Alcohol) Congestive heart failure 		

MRCPUK-part-2-march-2018: H/O borderline hypotension (BP: 95/70), COPD and AF. What is the most appropriate intervention?

- Digoxin 500 mg IV loading
 - B-blockers and verapamil are best avoided because of the potential for worsening hypotension here.

Atrial flutter

Tachycardia with a rate of 150/min ?atrial flutter

Overview

- Atrial flutter is a form of supraventricular tachycardia characterised by a succession of rapid atrial depolarisation waves.
- usually caused by a single macro reentrant rhythm within the atria.
- What is the differences between atrial flutter and focal atrial tachycardia?
 - ⇒ Atrial flutter is caused mechanistically by <u>macro</u>- reentry and has atrial rate (P wave/flutter morphology) <u>usually >250 bpm.</u>
 - ⇒ <u>Focal atrial tachycardia</u> is caused mechanistically by <u>micro</u>-reentry or <u>increased</u> automaticity and has atrial rates of 100-250 bpm.

Epidemiology

- Sex: ♂ > ♀ (5:2)
- Peak incidence: risk of atrial flutter increases with age

Etiology:

· similar to atrial fibrillation

ECG findings

- Regular, narrow QRS complexes
- flutter waves, which are a saw-tooth pattern of atrial activation
 - ⇒ most prominent in leads II, III, aVF, and V1.
- as the underlying atrial rate is often around 300/min the ventricular or heart rate is dependent on the degree of AV block. For example if there is 2:1 block the ventricular rate will be 150/min
- flutter waves may be visible following carotid sinus massage or adenosine

Management

- is similar to that of atrial fibrillation although medication may be less effective
- atrial flutter is more sensitive to cardioversion however so lower energy levels may be used
- Anticoagulate patients with atrial flutter similar to AF.
- Catheter ablation is the definitive treatment for atrial flutter.
 - radiofrequency ablation of the tricuspid valve isthmus is <u>curative</u> for most patients

Multifocal atrial tachycardia (MAT)

Multifocal atrial tachycardia has ≥ 3 P-wave morphologies on ECG

Definition

- it is an irregular cardiac rhythm caused by at least three different sites in the atria, which
 may be demonstrated by morphologically distinctive P waves.
- It is more common in elderly patients with chronic lung disease, for example COPD

Management

- correction of hypoxia and electrolyte disturbances
- · rate-limiting calcium channel blockers are often used first-line
- cardioversion and digoxin are not useful in the management of MAT

Atrial myxoma

Atrial myxoma - commonest site = left atrium

Overview

- · Benign cardiac tumor
- the most common primary cardiac tumors in adults.
 - (<u>rhabdomyoma</u> is the most common primary cardiac tumor in <u>pediatric</u> patients and strongly associated with tuberous sclerosis).
- 75% occur in **left atrium**, arising from a pedicle on the fossa ovalis.
- · more common in females
 - Three-quarters of cases of atrial myxoma occur in females
- Although most cases of atrial myxoma are sporadic, an autosomal dominant variety may also exist within families.
- 10% are inherited

Features

- · One third present with emboli
- One third with systemic inflammation (ESR ↑↑ in 1/3)
- One third are asymptomatic when detected.
- · There are 3 groups of manifestations:
 - 1. **Obstructive features**: like MS, signs vary with posture. Occasionally, there is a low-pitched sound called tumor plop.
 - Dyspnoea, (Exertional dyspnoea is present in three-quarters of patients).
 - Dizziness or syncope
 - results from the atrial myxoma obstructing the mitral valve.
 - **❖** Mitral valve obstruction is the most likely complication
 - Myxomas are more likely to have a stalk and be freely mobile.
 - atrial fibrillation
 - mid-<u>diastolic</u> murmur, 'tumour plop' (low-pitched sound)
 - murmur change with posture.
 - Elevated left atrial pressures cause dilatation.
 - 2. **Embolic features:** either systemic or pulmonary embolism.
 - 3. **Constitutional features**: such as fever, malaise, weakness, loss of weight, myalgia, arthralgia, clubbing, skin rash, Raynaud's phenomenon.

Investigations

 echo: pedunculated heterogeneous mass typically attached to the fossa ovalis region of the interatrial septum

- on histology
 - gelatinous appearance
 - abundant ground substance.

Treatment

· surgical removal by median sternotomy.

Prognosis

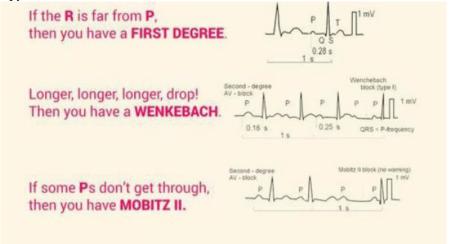
• sudden death may occur in 15% of patients.

Carney's complex is a familial multiple neoplasia and lentiginosis syndrome, associated with

- 1. Primary adrenal hypercortisolism
- 2. Lentigines and naevi of the skin
- 3. Various tumours including myxoma.

Heart block

Types of heart block

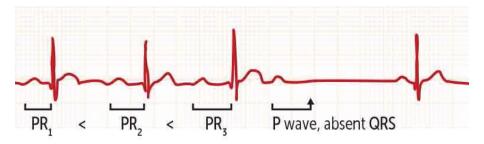


First-degree heart block

- PR interval > 0.2 seconds (> five small squares in the ECG.)
- Causes:
 - ⇒ Increased vagal tone (such as in trained athletes)
 - ⇒ Ischaemic heart disease
 - ⇒ Rheumatic fever
 - ⇒ Hyperkalaemia
 - ⇒ Hypokalaemia, and
 - ⇒ Drug therapy such as digoxin or beta-blockers.
- A long PR interval on the ECG may also be caused by structural abnormalities such as an atrial septal defect.
- No treatment is usually required.

Second-degree heart block

- Type 1 (Mobitz I, Wenckebach):
 - ⇒ progressive prolongation of the PR interval until a dropped beat occurs
 - ⇒ Mobitz Type I with symptoms is a **relative indication** for a permanent pacemaker
 - ⇒ Asymptomatic → NO treatment → Discharge him from the clinic
 - The risk of progression to complete heart block with Mobitz type I in an asymptomatic man is very low, unlike in Mobitz type II.



- Type 2 (Mobitz II):
 - ⇒ PR interval is constant, but the P wave is often not followed by a QRS complex
 - ⇒ the most appropriate next management step → Transvenous cardiac pacing
 - ⇒ Mobitz type II or complete heart block does not respond to atropine. Atropine may be useful for sinus or junctional bradycardia.
 - ⇒ In patients with Mobitz type II AV block, or complete heart block, a DDD or DDDR pacemaker is indicated.
 - DDD pacemaker will sense and pace both atria and ventricles.
 - DDD pacemakers ensure that the atrial and ventricles beat in synchrony thus preventing pacemaker syndrome.
- Second-degree heart block with RBBB implies that this patient has a significantly increased risk of complete heart block.
 - ⇒ prior to committing to pacemaker insertion, repeat tape is the most likely next step, with an electronic patient diary to see if the recorded arrhythmia corresponds to her symptoms.

Third degree (complete) heart block

Complete heart block causes a variable intensity of S1

Third degree (complete) heart block

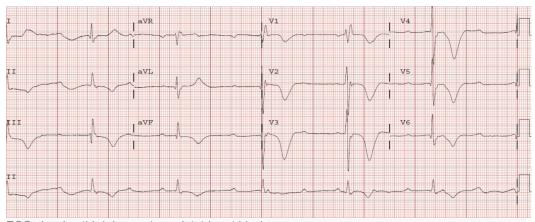
- there is no association between the P waves and QRS complexes
- Complete heart block (whether symptomatic or not) is an absolute indication for a permanent pacemaker

Causes

- · myocardial ischemia
 - ⇒ The most common cause of third degree atrioventricular block is <u>myocardial</u> ischemia.
 - Complete heart block is related most to <u>right coronary artery</u> occlusion because this commonly involves both the AV nodal artery and the right superior descending artery.
 - Prognosis is favourable, and revascularisation normally leads to restoration of sinus rhythm.
 - As the AV nodal artery arises proximally from the right ventricular artery, distal right coronary artery occlusion is not commonly associated with complete heart block.
 - the artery most likely to be affected → Proximal right coronary
 - ⇒ <u>Left coronary artery occlusion</u> leads to anterior myocardial infarction. As it is less commonly associated with complete heart block, when it does occur, the prognosis is very poor.
 - ⇒ Third degree atrioventricular block that is resulting from obstruction of the left anterior descending coronary artery is usually irreversible.
- Lyme disease
- Drugs eg: B. blockers
- Congenital third degree atrioventricular block might be due to maternal <u>lupus</u>.

Features

- Syncope
- heart failure
- regular bradycardia (30-50 bpm) that does not vary with exercise
- wide pulse pressure
- JVP: irregular cannon waves in neck
- variable intensity of S1
- compensatory increase in stroke volume with a large-volume pulse and systolic flow
- The escape rhythm of third-degree atrioventricular block resulting from obstruction of the right coronary artery is usually narrow-complex.
- the atrial rhythm is usually regular
- The bizarre, wide, inverted T-waves can be seen in Stokes-Adams attacks and do not necessarily imply new ischaemia.



ECG showing third degree (complete) heart block

Treatment

In patients with Mobitz type II AV block, or complete heart block, a DDD or DDDR pacemaker is indicated

- Asymptomatic or mild symptoms (stable)
 - ⇒ Condition-specific management
- Symptomatic (unstable): (syncope, ventricular rate is significantly low (<40 to 45 bpm) or low BP (mean arterial pressure <65 mmHg))
 - ⇒ Whilst arrangements are being made for temporary pacing, the options to be considered, prior to temporary transvenous pacing, in this context are:
 - 1. Atropine 0.5-1.0 mg intravenous bolus repeated as required up to 3mg.
 - 2. Isoprenaline, intravenous infusion at 2-10 microg/min.
 - it is a non-selective β agonist that is analog of epinephrine (adrenaline)
 - External cardiac pacing.
 - ⇒ temporary (transcutaneous or transvenous) pacing
 - Transvenous pacing is much more reliable than transcutaneous pacing
- Condition-specific management includes:
 - ⇒ treating acute coronary syndrome (i.e., antiplatelet medications, urgent revascularisation)
 - ⇒ medication toxicity (e.g., glucagon for beta-blocker toxicity, calcium for calciumchannel toxicity, or digoxin antibody for digitalis toxicity).
- Intravenous aminophylline is useful in complete heart block, as the heart block is often mediated by adenosine which aminophylline inhibits
- Post- MI:
 - ⇒ Following anterior MI → pace-maker insertion
 - ⇒ Following posterior MI and patient is haemodynamically stable → observation
 - Often spontaneously resolved

Pacemakers

Definition

 A permanent pacemaker is an implanted device that provides electrical stimuli, thereby causing cardiac contraction when intrinsic myocardial electrical activity is inappropriately slow or absent.

Conditions definitely needs a permanent pacemaker

- Symptomatic bradycardia due to sinus node dysfunction (sick sinus syndrome)
- Third-degree heart block
- second-degree (AV) block associated with any of the following:
 - ⇒ symptomatic bradycardia
 - ⇒ documented periods of asystole of 3 s or more
 - ⇒ any escape rate less than 40 bpm in awake, asymptomatic patients
 - type II second-degree AV block and a ventricular rate of 45 bpm when awake and asymptomatic
 - ⇒ asymptomatic sinus rhythm resulting in periods of asystole longer than 3.0 seconds
 - asystolic pause causing syncope.
 - dual chamber permanent pacemaker (DDDR).
 - The R in this code stands for responsive, and in an otherwise fit and well 76-year-old, he should have a responsive element to his PPM (that is, increases his heart rate with exercise).
 - ⇒ Type II second-degree AV block has a high chance of progressing to asystole (35%) each year
- Generally, permanent pacing can be justified for any degree of heart block associated with symptoms of bradycardia.

Indications for a temporary pacemaker

- symptomatic/haemodynamically unstable bradycardia, not responding to atropine
- post-ANTERIOR MI: type 2 or complete heart block
 - ⇒ post-INFERIOR MI complete heart block is common and can be managed conservatively if asymptomatic and haemodynamically stable
- trifascicular block prior to surgery
- Other indications for transvenous pacing in setting of acute MI are:
 - ⇒ asystole
 - ⇒ new bundle branch block (BBB) with first-degree heart block
 - ⇒ an old right BBB with first degree atrioventricular (AV) block and a new fascicular block

Notes

- All modern ICDs also function as pacemakers.
- Chest pain in Ventricular pacing
 - ⇒ Pacemaker rhythm may prevent interpretation of ST-segment changes and may require **urgent angiography** to confirm diagnosis.
 - ⇒ Reprogramming the pacemaker—allowing an evaluation of ECG changes during intrinsic heart rhythm—may be considered in patients who are not dependent on ventricular pacing, without delaying invasive investigation

Types of Pacemakers

- Pacemakers are classified by the nature of their pacing mode using a code of up to five letters
- The NBG Pacemaker code was developed by the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG):

1	II	Ш	IV	V
Chamber(s) Paced	Chamber(s) Sensed	Mode(s) of Response	Rate Modulation	Multisite Pacing
O = None	O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)		D = Dual (A+V)

Single-chamber pacemakers

- utilised for patients in permanent atrial fibrillation.
- VVI means there is **one lead in the ventricle** (pacing and sensing the ventricle, indicated by the 'VV').
- VVI pacemaker will pace and sense the right ventricle.
- VVI pacemaker is useful when we are not too concerned about atrial activity (e.g. in patients with atrial fibrillation).
- In the presence or organised atrial activity, a VVI pacemaker may pace the ventricles out of synch with the atria resulting in pacemaker syndrome.
 - ⇒ Since organised atrial activity is present, a **DDI pacemaker** would be preferred, as this **senses and paces both atria and ventricle to preserve synchrony.**

Dual-chamber pacemakers

- Have pacing electrodes in both the right atrium and the right ventricle.
- They allow maintenance of the physiological relationship between atrial and ventricular contraction and also allow the paced heart to follow the increase in sinus rate that occurs during exercise.

Biventricular pacemakers

- Pacemaker leads are placed in the right atrium, right ventricle and left ventricle.
- Useful in the management of patients with heart failure who have evidence of abnormal intraventricular conduction (most often evident as left bundle branch block (LBBB) on ECG) which causes deranged ventricular contraction or dyssynchrony.
- In a patient with severe ischaemic heart failure and is on optimal medical therapy.
 Despite this he is still symptomatic → ICD with biventricular pacing
 - ⇒ very prolonged QRS duration is indicating left dyssynchrony which is an indication for biventricular pacing according to NICE guidance.
 - ⇒ Documented VT in the context of ischaemic LV impairment necessitates the need for and a secondary prevention ICD.

Pacemaker complications

- Pacemaker complications are more common in the period following insertion.
- can be divided into early complications (<6 weeks) or late (>6 weeks).
- Most frequent complications are those related to implantation procedure, such as lead dislodgement and pneumothorax.
- pneumothorax can occur up to forty-eight hours following pacemaker insertion.
 - ⇒ It occurs in 1-2% of procedures and most patients will require chest drain insertion.
- The most common complication is **lead dislodgement** (higher rate atrial dislodgment than ventricular dislodgment).
- Lead dislodgement can occur following trauma or sporadically and can be either atrial or ventricular.
- Atrial dislodgment affects up to 3% of people whereas ventricular is less common affecting 1%.
- If the ECG shows loss of sensing and capture around the QRS complex → ventricular lead displacement in a dual chamber pacemaker.
 - What would be the likely ECG findings in ventricular lead displacement?
 Loss of sensing and capture of the QRS complex
- Atrial lead displacement would show an ECG with loss of atrial sensing and capture.
 - ⇒ The ECG in atrial lead displacement would show an ECG with loss of atrial sensing and capture in a dual chamber or single chamber pacemaker.
- On occasion lead displacement can be seen on chest X-Ray, however, it may not be seen, in this case →a lateral chest X-Ray may be of use in this scenario.
- Pacemaker syndrome would show AV dyssynchronisation.
- Subclavian vein obstruction is a fairly common complication over time but many patients may remain asymptomatic due to collateral vein formation. It can present with symptoms of superior vena cava (SVC) obstruction in severe cases.
- Twiddler's syndrome is when the patient intentionally or accidentally turns the pacemaker
 on its longitudinal axis which can cause lead dislodgement.
- Reel's syndrome is Twiddler's syndrome but on the horizontal axis.
- Pacemaker lead fracture
 - ⇒ occurs in 1-4% of pacemakers
 - ⇒ usually following excessive exercise or direct trauma.
 - ⇒ patient will require lead extraction and replacement.
- myocardial rupture:
 - ⇒ incidence is relatively small (<1%)

- ⇒ can be divided into early or late rupture with respect to the time it occurs following procedure.
- ⇒ Delayed perforations are less likely to cause such acute symptoms as well as a reduced incidence of tamponade and sudden cardiac death.
- ⇒ Risk factors for perforation include physician technique, patient independent factor (i.e obesity or difficult anatomy) and lead design.
- ⇒ presenting features :pericardial effusion, haemodynamically compromised following pacemaker insertion and is likely to develop cardiac tamponade and needs urgent intervention with pericardiocentesis.

Pacemaker syndrome

Pacemaker syndrome

- Loss of AV synchrony.
- Retrograde VA conduction.
- Absence of rate response to physiological need.

Pacemaker syndrome (breathlessness associated with ventricular pacing in the context of normal atrial activity).

VVI pacemaker will pace and sense the right ventricle. In the presence or organised atrial activity, a VVI pacemaker may pace the ventricles out of sync with the atria resulting in pacemaker syndrome.

Overview

- pacemaker syndrome is related to nonphysiologic timing of atrial and ventricular contractions, which may occur in a variety of pacing modes
- also named as "AV dyssynchrony syndrome."
- typically associated with a VVI pacemaker that results in simultaneous atria and ventricle conduction.

Risk factors

- Sick sinus syndrome as have preserved AV conduction.
- Single-chamber ventricular pacing.

Features

- Hypotension, tachycardia, tachypnoea, dizziness, syncope
- Ventricular contraction against closed tricuspid and mitral valves can result in raised JVP (pulsation and fullness in the neck) cannon waves

Complications of AV dyssynchrony:

Atrial fibrillation, thromboembolic events, and heart failure.

What are the characteristic ECG findings associated with this syndrome?

⇒ Small P waves with dissociation from QRS complex

Management

 In patients with other pacing modes, upgrading the pacemaker to a dual-chamber pacing or reprogramming the pacemaker parameters - eg, AV delay, post-ventricular atrial refractory period, sensing level, and pacing threshold voltage.

DC cardioversion in patients with pacemakers (eg: in AF)

- DC cardioversion is not contraindicated in patients with pacemakers
- Pacemaker function should be checked after cardioversion and antiarrhythmic therapy added

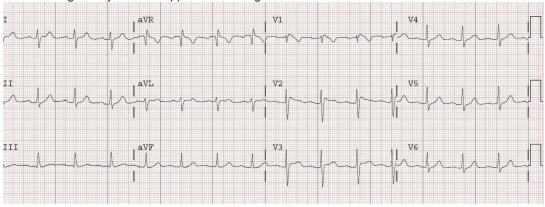
Brugada syndrome

Overview

- Inherited cardiovascular disease with may present with sudden cardiac death.
- Prevalence → 1:5,000-10,000.
- · More common in Asians.
- Autosomal dominant
- · A large number of variants exist
- Around 20-40% of cases are caused by a mutation in the SCN5A gene which encodes the myocardial sodium ion channel protein

ECG changes

- Convex ST segment elevation > 2mm in > 1 of V1-V3 followed by a negative T wave
- Partial right bundle branch block
- Changes may be more apparent following flecainide



ECG showing Brugada pattern, most marked in V1, which has an incomplete RBBB, a downsloping ST segment and an inverted T wave

Management

implantable cardioverter-defibrillator

<u>Catecholaminergic polymorphic ventricular tachycardia</u> (CPVT)

Overview

- CPVT is a form of inherited cardiac disease associated with sudden cardiac death.
- Inherited in an autosomal dominant fashion
- Prevalence of around 1:10,000.

Pathophysiology

- the most common cause is a defect in the ryanodine receptor (RYR2) which is found in the myocardial sarcoplasmic reticulum
- uncontrolled calcium release from the sarcoplasmic reticulum
- induced by adrenergic stress.

Features

- · exercise or emotion induced polymorphic ventricular tachycardia resulting in syncope
- · sudden cardiac death
- symptoms generally develop before the age of 20 years

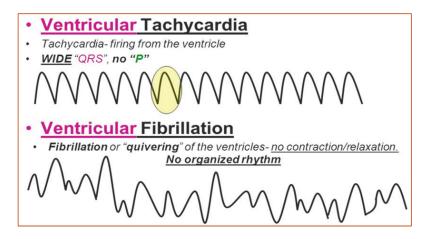
Management

- beta-blockers
- There is strong evidence that flecainide is effective when prescribed in addition to beta blockers
- implantable cardioverter-defibrillator
- · Left cervical sympathetic denervation
- All first-degree relatives should be evaluated with ECG, Holter monitoring and exercise stress testing.

Ventricular tachycardia

Definition

- wide QRS complex (duration >120 milliseconds) at a rate greater than 100 bpm, originating from a ventricular ectopic focus.
 - ⇒ Whilst a broad complex tachycardia may result from a supraventricular rhythm with aberrant conduction, the European Resuscitation Council advise that in a peri-arrest situation it is assumed to be ventricular in origin.
- It has the potential to precipitate ventricular fibrillation and hence requires urgent treatment. **Pathophysiology**
 - Among patients with prior MI or non-ischaemic cardiomyopathy, VT is usually due to reentry involving regions of slowed conduction adjacent to scar.
 - ⇒ Post MI ventricular tachycardia (VT) is most commonly due to scar tissue.
 - The definitive investigation would be → Electrophysiological study (EPS)
 - due to the fact that if this were scar related VT, the site could be localised and even possibly ablated.
 - If not, then an implantable cardiac defibrillator (ICD) implantation may be warranted if left ventricular (LV) dysfunction exists.
 - MADIT-2 trial showed a 5.6% 20-month absolute survival benefit in patients with LV dysfunction (EF<30%), post MI, treated prophylactically with an ICD.
 - (VT) may also arise from triggered activity due to early after-depolarisations (EADs)
 leading to torsades de pointes, a polymorphic ventricular tachycardia seen in the setting of
 a prolonged QT interval,
 - delayed after-depolarisations (DADs), which are seen in:
 - ⇒ idiopathic right ventricular outflow tract VT or
 - ⇒ catecholaminergic polymorphic VT
 - ➤ cellular abnormalities of calcium handling → Increased intracellular calcium → predispose to VT. especially during periods of sympathetic stimulation.
 - EADs occur during phase 2 or 3 of the action potential, whereas DADs occur during phase 4.
 - When an EAD or DAD reaches a 'threshold' potential, it can result in triggering of another action potential.
 - Ventricular tachycardia originates below the bundle of His.



Types: There are two main types of VT:

- Monomorphic VT
 - ⇒ organised, single-morphology QRS arising from one of the ventricles.
 - ⇒ most commonly caused by myocardial infarction
- Polymorphic VT
 - ⇒ multiple different wide QRS morphologies arising from one of the ventricles.
 - ⇒ results from abnormal myocardial repolarization.
 - ⇒ A subtype of polymorphic VT is <u>torsades de pointes</u> which is precipitated by prolongation of the QT interval. The causes of a long QT interval are listed below.

Other classifications of VT

- Sustained VT
 - ⇒ A ventricular rhythm faster than 100 bpm lasting at least 30 seconds or requiring termination due to haemodynamic instability.
 - ⇒ almost always symptomatic.
- Non-sustained VT
 - ⇒ A ventricular rhythm faster than 100 bpm lasting for at least 3 consecutive beats but terminating spontaneously in less than 30 seconds, and not resulting in significant haemodynamic instability.
 - ⇒ If these do not cause any haemodynamic compromise, **treatment is not needed.**
 - ⇒ The most appropriate next step → Check potassium and magnesium levels
 - During the GISSI-2 trial it was observed that a serum K⁺ level of <3.6 mmol/l was associated with a twofold increased risk of VF. Therefore serum K⁺ should be maintained >4 mmol/l by oral or intravenous (IV) supplementation in patients with acute MI.
 - Concomitant magnesium (Mg²⁺) deficiency is present in many patients with hypokalaemia and also makes correction of hypokalaemia difficult. Hence serum Mg²⁺ levels should also be checked and maintained >1 mmol/l.

Feature

- Patients may have a normal cardiac output or may be haemodynamically compromised
- Sustained VT is usually observed in ischaemic cardiomyopathy, but idiopathic VT may also be observed in patients without structural heart disease.
- jugular veins may show cannon A waves due to atrioventricular dissociation.

Differential diagnosis

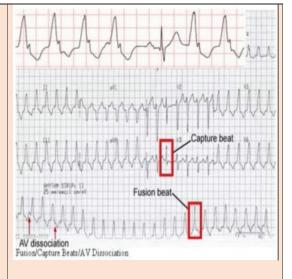
- Supraventricular tachycardia with bundle-branch block may resemble ventricular tachycardia on the ECG
 - ⇒ 80% of all broad complex tachycardias are secondary to VT and the proportion is even higher in patients with structural heart disease.
 - ⇒ In all cases of doubt, the rhythm should be treated as a VT.
 - the safest course of action is to consider a drug like adenosine, which will cause short-lived AV block in SVT but not in VT. It is the presence of aberrant conduction which can lead to diagnostic confusion.
 - Amiodarone may be an appropriate next step for cardioversion, once the underlying rhythm has been elucidated.
- Features suggesting VT rather than SVT with aberrant conduction
 - ⇒ AV dissociation
 - ⇒ fusion or capture beats
 - positive QRS concordance in chest leads ((same polarity QRS direction in all chest leads V1 -V6) (Absence of an RS complex in all pre-cordial leads, i.e., all the leads are concordant)
 - ⇒ marked left axis deviation
 - ⇒ history of IHD
 - ⇒ lack of response to adenosine or carotid sinus massage
 - ⇒ very broad QRS > 160 ms
 - ⇒ bifid upright QRS with a taller first peak in V1
 - ⇒ deep S wave in V6

Capture beats

- intermittent narrow QRS complex owing to normal ventricular activation via the AV node
- occurs when a supraventricular and a ventricular impulse coincide to produce a hybrid complex.
- It indicates that there are two foci of pacemaker cells firing simultaneously: a supraventricular pacemaker (e.g. the sinus node) and a competing ventricular pacemaker (source of ventricular ectopics).
- Causes:
 - ⇒ Ventricular tachycardia
 - ⇒ Accelerated idioventricular rhythm (AIVR)

fusion beats

(intermediate between ventricular tachycardia beat and capture beat) are seen





Fusion beats due to VT - the first of the narrower complexes is a fusion beat (the next two are capture beats)

Management

VT: cardioversion treatment

- ⇒ VT with pulse (not respond to medical treatment) → LOW ENERGY synchronized cardioversion
 - Synchronization avoids the delivery of a LOW ENERGY shock during cardiac repolarization (t-wave). If the shock occurs on the t-wave (during repolarization), there is a high likelihood that the shock can precipitate Ventricular Fibrillation (VF).
- **⊃** Pulseless VT or VF → HIGH ENERGY asynchronized cardioversion
- If the patient has adverse signs (systolic BP < 90 mmHg, <u>chest pain</u>, heart failure or rate > 150 beats/min) then immediate cardioversion is indicated.
 - ⇒ anaesthetist needs to be called to assist with direct current cardioversion (DCCV)
 which should be 'synchronised' to limit the risk of conversion to VF.
 - usually at a starting energy dose of 100 J (monophasic; comparable biphasic recommendations are not currently available).
 - ⇒ If deteriorate in the meantime and become pulseless, then a precordial thump should be given, followed immediately by DCCV if not successful.
 - ⇒ In cases of pulseless VT, the electrical cardioversion should be unsynchronized.
 - Amiodarone is the drug of choice for acute VT refractory to cardioversion shock.
 - ➡ Unstable polymorphic VT is treated with immediate defibrillation. The defibrillator may have difficulty recognizing the varying QRS complexes; therefore, synchronization of shocks may not occur.
- In stable patients (absence of adverse signs):
 - ⇒ stable patients stable patients with monomorphic VT and normal LV function,
 - If LV function is impaired, amiodarone (or lidocaine) is preferred to procainamide for pharmacologic conversion because of the latter drug's potential for exacerbating heart failure.
 - restoration of sinus rhythm is typically achieved with IV procainamide, amiodarone, or sotalol.
 - ➡ If LV function is impaired, amiodarone (or lidocaine) is preferred to procainamide for pharmacologic conversion because of the latter drug's potential for exacerbating heart failure
 - ⇒ In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with **synchronised DC** shocks
 - ⇒ If medical therapy is unsuccessful, synchronized cardioversion (50-200 J monophasic) following sedation is appropriate.
 - prophylactic implantable cardioverter defibrillator implantation is recommended in high-risk patients.

- Polymorphic VT in stable patients
 - ⇒ typically terminates on its own.

	Unsynchronized	Synchronized
When to deliver electricity	At any point in cycle	Not during the T-wave
Indications	V-fib, pulseless VT	Everything except V-fib and pulseless VT

Drug therapy

Verapamil is contra-indicated in VT because it can cause a catastrophic fall in blood pressure.

- Amiodarone: ideally administered through a central line
 - (i.e. given after the third shock). If amiodarone is not available lidocaine is a suitable alternative.
- Lidocaine: use with caution in severe left ventricular impairment
- Procainamide
- Adenosine is useful diagnostically when the diagnosis of regular wide complex tachycardia
 is in doubt.
- Verapamil should NOT be used in VT

Sotalol is recommended as the first-choice drug to prevent a recurrence of ventricular tachycardia (VT)

If drug therapy fails

- electrophysiological study (EPS)
- implant able cardioverter-defibrillator (ICD) this is particularly indicated in patients with significantly impaired LV function

C.V Resuscitation:

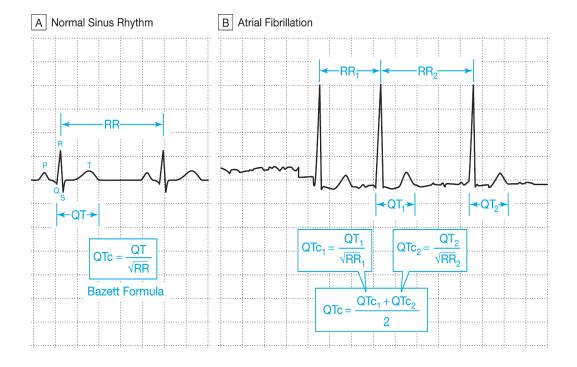
- Guidelines from the Resuscitation Council (UK) state that if a patient has a monitored and witnessed VF/VT arrest in hospital, three quick successive (stacked) shocks should be given. Chest compressions should be started immediately after the third, with a compression to ventilation ratio of 30:2 for 2 minutes.
- A precordial thump can be successful if given within seconds of the onset of a shockable rhythm. Delivery should not delay calling for help, or accessing a defibrillator, but would be indicated here whilst awaiting the defibrillator. Chest compressions should start immediately if it is unsuccessful.
- Intravenous adrenaline would be given every 3-5 minutes once chest compressions had started.

QT interval

QT interval: Time between the start of the Q wave and the end of the T wave

- Definition
 - QT measured from the start of the QRS complex to the end of the T wave
 - represents the duration of activation and recovery of the ventricular myocardium
- Normal duration → should be between 0.33 and 0.44 seconds
- Corrected QT interval (QTc) is calculated by dividing the QT interval by the square root of the preceding R R interval. Normal = 0.42 s.

$$QTcB = \frac{QT}{\sqrt{RR}}$$



Long QT syndrome

Definition

- Long QT syndrome (LQTS) is an inherited condition associated with delayed repolarization
 of the ventricles.
- A normal corrected QT interval is less than 430 ms in males and 450 ms (0.45 s) in females.
 - One large box represents 200 ms, one small box represents 40 ms

Mechanism

Long QT syndrome - usually due to loss-of-function/blockage of K+ channels

- the usual mechanism by which drugs prolong the QT interval is blockage of potassium channels → <u>delayed repolarization</u> of the ventricles.
- Most drugs that prolong the QT_c interval act by blocking hERG-encoded potassium channels, although some drugs modify sodium channels.
- The most common variants of LQTS (LQT1 & LQT2) are caused by defects in the alpha subunit of the slow delayed rectifier potassium channel.

Epidemiology

• more common in females.

Classification

	LQT1	LQT2	LQT3
Gene	KCNQ1	KCNQH2/ hERG	SCN5A
Iron	K s (redifier potassium current, s low component)	K r (redifier potassium current, r apid component)	Na
Pathophysiology	Decreased potassium outward current	Decreased potassium outward current	excessive sodium inward current
Triger of arrhythmia	Exercise stress	Emotional stress	Rest
Occurrence	> 50%	34 – 40%	10 – 15%

Causes of a prolonged QT interval

Methadone is a common cause of QT prolongation

Anti- arrhythmics	Antihistamines	Anti- infectives	Antimalarials
Amiodarone Disopyramide Dofetilide Ibutilide Procainamide Quinidine Sotalol	Astemizole Terfenadine	Clarithromyci n Erythromycin Pentamidine Sparfloxacin	Chloroquine Halofantrine
Antipsychotic s	Gastro-intestinal drugs	Opiate agonists	Other drugs
Chlorpromazine Haloperidol Mesoridazine Pimozide Thioridazone	Cisapride* Domperidone	Levomethady I Methadone	tricyclic antidepressant s, fluoxetine Arsenic trioxide Bepridil Droperidol Probuco
Congenital	Other conditions		
Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel) Romano-Ward syndrome (no deafness)	□ Electrolytes:		

- *Cisapride have been withdrawn worldwide due to risk of QT prolongation
- Jervell-Lange-Nielsen syndrome:
 - rincludes deafness and is due to an abnormal potassium channel
 - autosomal recessive
 - caused by Mutations in the KCNE1 and KCNQ1 genes
 - Mutations in the KCNE1 and KCNQ1 genes → abnormal potassium channel
 → abnormal functions of inner ear structures and cardiac muscle.
- Romano-Ward syndrome:
 - congenital long QT syndrome
 - autosomal dominant
 - involves only cardiac (<u>no</u> deafness)
- The human ether-à-go-go related gene (hERG) is the gene affected by drugs that lengthen QT interval inadvertently; erythromycin, terfenadine, and ketoconazole.

 a non-sedating antihistamine are classic cause of prolonged QT in a patient, especially if also taking P450 enzyme inhibitor, e.g. Patient with a cold takes terfenadine and erythromycin at the same time

Features

A QT interval of greater than 0.44 seconds is associated with the development of ventricular arrhythmia, syncope and sudden cardiac death.

- asymptomatic
- · may be picked up on routine ECG or following family screening
- Long QT1 usually associated with exertional syncope, often swimming
- Long QT2 often associated with syncope occurring following emotional stress, exercise or auditory stimuli
- · Long QT3 events often occur at night or at rest
- · sudden cardiac death

Diagnosis

- corrected QT interval
 - Diagnosis is based upon the QTc (corrected QT interval),
 - QTc may be within the normal range at rest; hence Holter ECG monitoring is recommended.
- genetic testing of LQTS
 - Identification of an LQTS genetic mutation confirms the diagnosis.
 - However, a negative result on genetic testing is of limited diagnostic value because only approximately 50% of patients with LQTS have known mutations. The remaining half of patients with LQTS may have mutations of yet unknown gene. Therefore genetic testing of LQTS has high specificity but a low sensitivity.

Complications

may lead to ventricular tachycardia → collapse/sudden death.

Management

Congenital long QT syndrome:

- Beta-blockers
 - Beta-blockers are first-line initial treatment
 - Beta blockers alone are enough to abate collapses in up to 70% of patients.
 - Beta blockers act by:
 - 1. decrease sympathetic activation from the left stellate ganglion,
 - 2. also decrease the maximal heart rate achieved during exertion and thereby prevent exercise-related arrhythmic events that occur in LQTS.
 - should be avoided in those congenital cases in which bradycardia is a prominent feature.
 - note sotalol may exacerbate long QT syndrome (due to blockage of K channel). This can be a particular risk in individuals with hypokalaemia. Therefore Sotalol is better to be avoided in patients with thiazide diuretics.
- patients who remain symptomatic despite receiving the maximally tolerated dose of betablockers → **Permanent pacing and** can be used in addition to beta-blockers.
- patients who remain refractory to beta-blockade and pacing → High left thoracic sympathectomy

- Implantable cardioverter-defibrillators (ICDs) are useful in rare instances when torsades still continues despite all of these treatments.
- Beta-blockers should be used along with ICDs because shock can further precipitate torsades by adrenergic stimulation.
- Left stellate cardiac ganglionectomy is an invasive procedure and results in Horner's syndrome. It is performed in patients who have symptoms despite βB and have frequent shocks with ICD.

Acquired long QT syndrome

- avoid drugs which prolong the QT interval and other precipitants if appropriate (e.g. Strenuous exercise)
- Long-term treatment in acquired cases is usually not required because the QT interval returns to normal once the predisposing factor has been corrected.
- · Correction of any electrolyte disturbance
 - Due to the pseudo-obstruction it is very likely that the patient is hypokalaemic and as such this is the first reversible aetiology for the non-sustained VT that needs to be investigated
 - ❖ → Check electrolytes
 - Checking Magnesium would also be an appropriate step.
- Beta-blockers are contra-indicated in acquired cases because bradycardia produced by these agents can precipitate torsades. They should also be avoided in those congenital cases in which bradycardia is a prominent feature.
- · Pacemaker implantation is effective in cases that are associated with heart block or bradvcardia.
- ICDs are indicated in cases that cannot be managed by avoidance of any specific precipitating factor.

QT shortening: caused by:

- Hypercalcaemia
- Hypermagnesaemia
- Digoxin
- Thyrotoxicosis.

January 2019 exam: A patient develops torsades de pointes shortly after being started on sotalol. What effect does sotalol have on the cardiac cell membrane to make this more likely? Blockage of potassium channels → prolonged QT interval.

Torsades de pointes (TdP)

Overview

- Torsades de pointes ('twisting of the points') is a rare arrhythmia associated with a long QT interval.
- It may deteriorate into ventricular fibrillation and hence lead to sudden death
- In its most typical form, sudden slowing of heart rate (i.e., pauses) invariably precede each burst of TdP, and the recurrent arrhythmia is referred to as "pause-dependent TdP"

Risk factors

- Female sex
- causes of QT prolongation,
- R-on-T phenomenon
 - the R-wave, representing ventricular depolarization, occurs during the relative refractory period at the end of repolarization (represented by the latter half of the Twave).

- Long QT intervals predispose the patient to an R-on-T phenomenon,
- R-on-T can initiate torsades.
- bradycardia,
- congestive heart failure,
- · digitalis therapy,
- severe alkalosis
- recent conversion from atrial fibrillation.

Management

- Stop all drugs which prolong QT
- Correct any electrolyte abnormalities
- IV magnesium sulphate (MgSo4)
 - the best initial drug
 - Mode of action: MgSo4 → ↓ Ca influx → ↓ amplitude of the VT and helping terminate runs of torsade's.
 - Dose: 2 gm as bolus over 10 minutes, followed by another bolus in 15 minutes if required, or continuous infusion at a rate of 5-20 mg/min.
 - It is effective even when serum magnesium level is normal.
- Temporary pacemaker/transvenous overdrive pacing (atrial or ventricular)
 - reserved for patients with long QT-related TdP who do not respond to intravenous magnesium.
- Isoproterenol
 - usually used as a temporizing measure prior to pacing in patients who have failed to respond to magnesium and are awaiting placement of a temporary pacemaker.

Adult advanced life support

Resuscitation Council (UK) 2021 guidelines

Major points include:

- Point-of-care ultrasound (POCUS)
 - ⇒ The guidelines recognise the increasing role of point-of-care ultrasound (POCUS) in peri-arrest care for diagnosis, but emphasises that it requires a skilled operator, and the need to minimise interruptions during chest compression.
 - ⇒ POCUS may be useful to diagnose treatable causes of cardiac arrest such as cardiac tamponade and pneumothorax.
 - ⇒ Right ventricular dilation in isolation during cardiac arrest should not be used to diagnose massive pulmonary embolism.
- Immediately after the first shock (and each subsequent shock) chest compressions should be restarted immediately and pulse and rhythm reassessed after two minutes.
- Chest compression
 - ⇒ Ratio of chest compressions to ventilation is 30:2
 - ⇒ Chest compressions are now continued while a defibrillator is charged
 - ⇒ After each shock chest compressions should be restarted immediately before anything else is done.

Adrenaline

- should be used as soon as possible when the cardiac arrest rhythm is nonshockable
- ⇒ after 3 defibrillation attempts for a shockable cardiac arrest rhythm.
- during a VF/VT cardiac arrest, adrenaline 1 mg is given once chest compressions have restarted after the third shock and then every 3-5 minutes (during alternate cycles of CPR).
- ⇒ A 1 mg dose of adrenaline (epinephrine) would be administered with:
 - 0.1 ml of 1 in 100,
 - 1 ml of 1 in 1000 and
 - 10 ml of 1 in 10.000.
- ⇒ 10 ml of 1 in 10,000 is the recommended dose and concentration by the UK Resuscitation Council.
- ➡ If not able to gain any venous access within two minutes → Obtain intraosseous access (it provides adequate plasma levels of drugs and allows equivalent flow rates to IV access).
- ⇒ Delivery of drugs via a tracheal tube is no longer recommended

Antiarrhythmic drugs (in VF/ pulseless VT)

- ⇒ Give Amiodarone 300 mg after the third shock and 150 mg after the fifth shock.
- \Rightarrow If amiodarone is not available \rightarrow use Lidocaine 100 mg after the third shock and 150 mg after the fifth shock.
- Atropine is no longer recommended for routine use in asystole or pulseless
- Thrombolytic drugs
 - Consider thrombolytic drug therapy when pulmonary embolus is the suspected or confirmed as the cause of cardiac arrest.
 - ⇒ Consider CPR for 60-90 minutes after administration of thrombolytic drugs.

Waveform capnography during advanced life support

- ⇒ Use waveform capnography to confirm correct tracheal tube placement during CPR.
- ⇒ Use waveform capnography to monitor the quality of CPR.
- ⇒ An increase in ETCO2 during CPR may indicate that ROSC has occurred. However, chest compression should not be interrupted based on this sign alone.

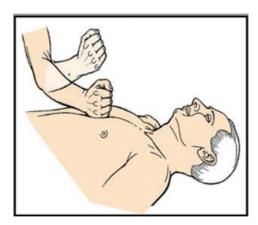
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Recurrent or refractory VF

- ⇒ Consider escalating the shock energy, after a failed shock and for patients where refibrillation occurs.
- ⇒ For refractory VF, consider using an alternative defibrillation pad position (e.g. anterior- posterior).

Precordial thump

- ⇒ Indicated only in witnessed or monitored cardiac arrect whilst awaiting the defibrillator within seconds of the onset of a shockable rhythm.
- ⇒ It has a very low success rate for cardioversion. There is more success with pulseless VT than with VF.
- ⇒ Chest compressions should start immediately if it is unsuccessful.
- ⇒ The ulnar edge of a tightly clenched fist is used to deliver a sharp impact from a height of about 20 cm, then retract immediately (thereby creating an impulse-like stimulus). It delivers approximately 7-10 joules of energy.
- ⇒ Only one thump should be delivered over the lower third of the sternum. Repeating a precordial thump is not recommended.



Electrical activity (PEA)

⇒ pulseless with no respiratory effort , ECG reveals small complexes with a normal morphology → CPR + Adrenalin 1mg repeated every 3-5 minutes

Defibrillation

- ⇒ Defibrillation is used to convert ventricular fibrillation to sinus rhythm
- ⇒ Use single shocks where indicated, followed by a 2 minute cycle of chest compressions.
- ⇒ The use of up to three-stacked shocks may be considered only if initial ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) occurs during a witnessed, monitored cardiac arrest with a defibrillator immediately available e.g. during cardiac catheterisation or in a high-dependency area.
- ⇒ Antero-lateral pad position is the position of choice for initial pad placement. Ensure that the apical (lateral) pad is positioned correctly (mid-axillary line, level with the V6 ECG electrode position) i.e. below the armpit.
- ⇒ In patients with an implantable device, place the pad > 8 cm away from the device
- ⇒ Range of the initial defibrillation energy
 - No clear evidence so, any level from 120-360 J is acceptable followed by a fixed or escalating strategy up to maximum output of the defibrillator.

Cardiac arrest in profound hypothermia

- ⇒ Prolonged cardiopulmonary resuscitation with re-warming is the management of choice.
- ⇒ Recovery with intact neurology has been reported even after very prolonged arrests, therefore resuscitation should be continued for far longer than would normally be considered.
- ⇒ Hypothermic patients do not respond well to shocks or drugs and if there is no response to the first three shocks the patient should be rewarmed to at least 32°C before any drugs or shocks are administered.

Management of cold water drowning

- patients should be lifted out of the water in the prone position
- Re-warming such patients should be undertaken in a hospital that has extracorporeal re-warming facilities
- Defibrillation is ineffective if the myocardium is cold
- ⇒ Hypothermia may render the carotid pulse impalpable so it is important to commence chest compression with firm evidence of cardiac arrest.
- ⇒ Continuous chest compression should be applied throughout transportation, which is as effective as chest compression with expired air resuscitation

Lance-Adams syndrome (Post-hypoxic myoclonus)

- Definition: a rare condition that can occur following a period of cerebral hypoxia (e.g. post cardiac arrest)
- Onset: occurs within days to weeks of cardiac arrest.
- Characterised by intention myoclonus.
- Treatment: antiepileptics (e.g. levetiracetam, valproate)

Peri-arrest arrhythmias

Resuscitation Council (UK) 2021 guidelines

Tachycardia

- To convert atrial or ventricular tachyarrhythmias, the shock must be synchronised to occur with the R wave of the ECG.
- For atrial fibrillation:
 - ⇒ An initial synchronised shock at maximum defibrillator output rather than an escalating approach is a reasonable strategy
- For atrial flutter and paroxysmal supraventricular tachycardia:
 - ⇒ Give an initial shock of 70 120 J **and** stepwise increase energy for subsequent
- For ventricular tachycardia with a pulse:
 - ⇒ Give an initial shock of **120-150 J and** stepwise increase energy for subsequent shocks
- If cardioversion fails to restore sinus rhythm and the patient remains unstable:
 - ⇒ give IV amiodarone 300 mg over 10–20 minutes (or procainamide 10–15 mg kg-1 and re-attempt electrical cardioversion.
 - ⇒ The loading dose of amiodarone can be followed by an infusion of 900 mg over 24 hours.

Bradycardia

- 1st line: give atropine 500 mcg IV (IO) and, if necessary, repeat every 3–5 minutes to a total of 3 mg.
- 2nd line (If atropine is ineffective): isoprenaline (5 mcg min⁻¹ starting dose), and adrenaline (2–10 mcg min⁻¹).
- For bradycardia caused by inferior myocardial infarction, cardiac transplant or spinal cord injury, consider giving aminophylline (100–200 mg slow intravenous injection).
- If bradycardia caused by beta-blockers or calcium channel blockers → give glucagon
- · For bradycardia in patients with cardiac transplants
 - **⇒** Give aminophylline
 - ⇒ **Do not give atropine**, it can cause a high-degree AV block or even sinus arrest.
- For bradycardia refractory to drug therapies in patients who are unstable:
 - ⇒ transcutaneous pacing
 - ⇒ If transcutaneous pacing is ineffective, consider transvenous pacing.
- If atropine is ineffective and transcutaneous pacing is not immediately available, fist pacing can be attempted while waiting for pacing equipment.

Wolff-Parkinson White (WPW)

Pathophysiology

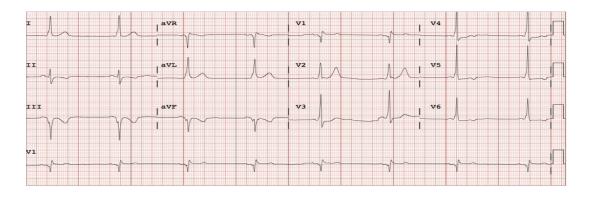
 Due to a congenital accessory conduction pathway, called the <u>bundle of Kent</u>, that connects the atria to the ventricles, bypassing the AV node and leading to <u>ventricular</u> <u>preexcitation</u>. As the accessory pathway does not slow conduction, AF can degenerate rapidly to VF

Presentation

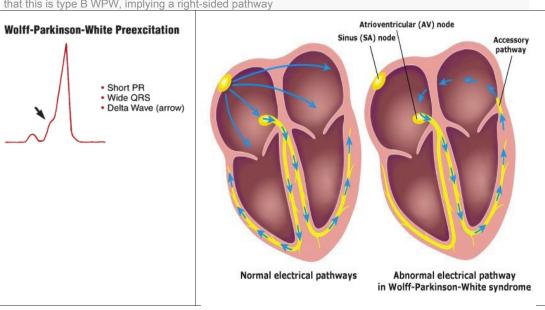
- Most patients are asymptomatic.
- WPW presents as SVT that can alternate with ventricular tachycardia (VT).
- SVT is the most common type of tachycardia seen in a patient with WPW.
 - ⇒ often present with AV re-entrant tachycardia
- The other main clue to the diagnosis is worsening of SVT after the use of calcium blockers or digoxin

Possible ECG features

- short PR interval
- wide QRS complexes with a slurred upstroke 'delta wave' (can be associated with negative delta waves in II, III and aVF)
- ECG in sinus rhythm reveals right bundle-branch block
- left axis deviation if right-sided accessory pathway*
 - ⇒ *in the majority of cases or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation
- right axis deviation if left-sided accessory pathway
- non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia.



ECG showing short PR interval associated with a slurred upstroke (delta wave). Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia. The left axis deviation means that this is type B WPW, implying a right-sided pathway



Differentiating between type A and type B

- type A (left-sided pathway): dominant R wave in V1
- type B (right-sided pathway): no dominant R wave in V1
 - ⇒ In type B pre-excitation, the accessory pathway connects the right atrium to the right ventricle
- there is a rare type C WPW, WPW in which the delta waves are upright in leads V1-V4 but negative in leads V5-V6

Associations of WPW

- **HOCM**
- mitral valve prolapse
- Ebstein's anomaly
- thyrotoxicosis
- secundum ASD
- Leber's hereditary optic neuropathy (mitochondrial disease)

Investigations

- ECG
 - ⇒ Short PR interval
 - ⇒ ECG delta wave: a slurred upstroke at the start of the QRS complex, secondary to preexcitation
 - ⇒ Widened QRS
- The most accurate test is electrophysiologic studies

Management

Acute episodes

- Hemodynamically unstable: electrical cardioversion
- Hemodynamically stable: assess underlying rhythm
 - ⇒ Narrow-complex tachycardia (including Afib, atrial flutter)
 - Rhythm control measures (i.e. IV procainamide or cardioversion) are the safest treatment option.
 - Vagal maneuvers and AV nodal blocking agents (Adenosine, B-Blockers, Calcium Channel Blockers, Digoxin) are contraindicated (may precipitate ventricular tachycardia or V-fib)
 - ⇒ Wide-complex regular or irregular tachycardia → Determine whether the rhythm is more likely to be ventricular or supraventricular in origin (e.g., Brugada criteria)
 - VT (~80%): pharmacological cardioversion or synchronized electrical cardioversion
 - SVT (< 20%): Determine if an accessory pathway is present.
 - Findings suggestive of an accessory pathway: synchronized electrical cardioversion or IV procainamide
 - ☐ HR > 200
 - Irregular rhythm
 - No bundle branch block on ECG
 - Signs of impending instability (e.g., clammy skin)
 - Baseline ECG findings that support the diagnosis
 - No signs of an accessory pathway: manage as SVT
 - Undifferentiated wide-complex tachycardia: Treat as VT, with either electrical cardioversion or IV procainamide

Long-term management

- High-risk patients → Catheter ablation
 - ⇒ Syncope
 - Associated atrial fibrillation, atrial flutter, or atrial tachycardia
 - ⇒ Aborted sudden cardiac death
 - ⇒ Family history of sudden cardiac death
 - ⇒ High-risk occupations (e.g., pilots, athletes, school bus driver)

Low-risk patients

- ⇒ Asymptomatic patients: usually no treatment required
- ⇒ symptomatic patients: First-line treatment → catheter ablation

Differentiating between VT and SVT

Brugada criteria				
ECG finding	VT	SVT		
Absence of RS in all precordial leads?	Yes	No		
R:S interval > 100 ms in one precordial lead?	Yes	No		
Signs of AV dissociation present?	Yes	No		
QRS morphology consistent with VT in leads V ₁₋₂ and V ₆ ?	Yes	No		
Interpretation	<u> </u>			

Interpretation

- If the answer to any is yes: most likely VT
- If none are present: most likely SVT

WPW management

- Asymptomatic : (incidentally found delta wave on ECG) → Reassurance
- Asymptomatic in high-risk professions (eg pilots, school bus driver) is best managed by catheter ablation of the accessory pathway
- Asymptomatic WPW in someone with a <u>family history of sudden cardiac death</u> is another indication for radiofrequency catheter ablation
- Chronic medical therapy: flecainide, amiodarone, procainamide
- Definitive treatment: radiofrequency ablation of the accessory pathway (first-line therapy)

Contraindications in WPW

A simple mnemonic to remember for drugs to avoid in WPW syndrome is ABCD (Adenosine, B-Blockers, Calcium Channel Blockers, Digoxin).

- Digoxin
- Beta-blockers
- Diltiazem, verapamil
- Amiodarone
- This is because blocking the AV node may enhance the rate of conduction through the
 accessory pathway, increasing the ventricular rate and potentially deteriorating into
 ventricular fibrillation.

If it is not possible to quickly identify the underlying rhythm as SVT or VT, it is safest to treat empirically as VT with synchronized electrical cardioversion (100 J) or with IV

If wide-complex tachycardia is present and the diagnosis of ventricular tachycardia (VT) cannot be excluded, the drugs of choice are IV procainamide or amiodarone.

Lown-Ganong-Levine (LGL) syndrome:

LGL syndrome is like WPW in the sense that it is a pre-excitation syndrome. However, the ECG changes present is only short PR interval without delta waves or abnormal QRS complex.

Implantable cardiac defibrillators (ICD)

Indications

- Congenital long QT with family history of sudden cardiac death at young age.
- hypertrophic obstructive cardiomyopathy (HOCM)
- · previous cardiac arrest due to VT/VF
- Sustained VT causing haemodynamic compromise
- previous myocardial infarction with non-sustained VT on 24 hr monitoring, inducible VT on electrophysiology testing and ejection fraction < 35%
- Brugada syndrome
- Arrhythmogenic right ventricular cardiomyopathy causing cardiac arrest.

Acute pericarditis

Overview

- Acute pericarditis: inflammation of the pericardium that either occurs as an isolated process or with concurrent myocarditis (myopericarditis).
- Pericarditis is one of the differentials of any patient presenting with chest pain.

Features

- Pleuritic chest pain
 - Exacerbated by inspiration and lying flat, relieved by sitting up and leaning forwards
- Shoulder pain (referred pain): pericarditis is innervated by phrenic nerve
- Pericardial rub (present in 50% of cases.) → pathognomic feature
- Other symptoms include non-productive cough, dyspnoea and flu-like symptoms

Types and causes

- Fibrinous pericarditis (the most common type)
 - ⇒ Causes:
 - Viral infection is the most common cause of acute pericarditis: the most common viral cause is Coxsackie B virus
 - Acute myocardial infarction (MI): more common than dressler syndrome
 - friction rub is more common than pain
 - Aspirin is the only NSAID that can be used in pericarditis complicating MI.
 - Post MI (Dressler syndrome): rare, autoimmune-mediated phenomenon to myocardial antigens, occur 2 – 4 weeks post MI
 - Because of the risk of hemorrhagic pericarditis, anticoagulant therapy should be stopped in patients with dressler syndrome.
 - Radiation, trauma, severe infections
 - Uremic pericarditis
 - blood urea nitrogen (BUN) level is usually greater than 60 mg/dL (22 mmol/L).
 - Hemorrhagic effusions are more common and result in part from uremiainduced platelet dysfunction.
 - does not present with the classic diffuse ST-elevations seen on ECG as in other types of pericarditis.
 - Uremic pericarditis is an indication for urgent hemodialysis.

Serous pericarditis

- Usually caused by noninfectious inflammation such as: rheumatoid arthritis (RA) systemic lupus erythematosus (SLE).
- ⇒ Fibrous adhesions rarely occur.
- Purulent or suppurative pericarditis
 - ⇒ Most commonly caused by staphylococcal and gram-negative species,
 - ⇒ high percentage of patients develop constrictive pericarditis.
- Hemorrhagic pericarditis
 - ⇒ Most commonly caused by:
 - tuberculosis, direct neoplastic invasion.
 - Severe bacterial infections
 - Bleeding diathesis, cardiac surgery or trauma (may cause tamponade).

Caseous pericarditis

- caseation within the pericardial sac is tuberculous in origin, until proven otherwise.
- ⇒ In tuberculous pericarditis, fever, night sweats, and weight loss are commonly noted (80%).
- ➡ Untreated, caseous pericarditis is the most common antecedent to chronic constrictive pericarditis of a fibrocalcific nature.
 - Approximately 50% of affected patients develop constrictive pericarditis.

ECG changes

- Stage 1 (initial)
 - ⇒ **Diffuse** ST elevations
 - ⇒ ST depression in aVR and V1
 - ⇒ PR segment depression (most specific ECG marker for pericarditis)
- Stage 2: ST segment normalizes in ~ 1 week.
- Stage 3: inverted T waves in all leads ~ 1 − 2 weeks
- Stage 4: ECG returns to normal baseline after weeks to months.

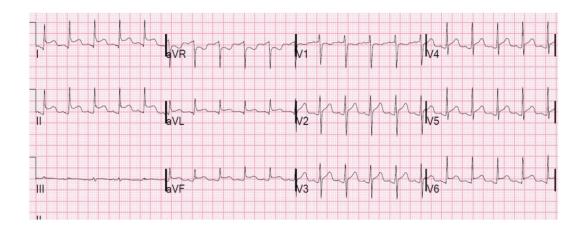
Which ECG changes would you expect to see in the next week or two?

⇒ T-wave inversion in all leads

Echocardiography is often normal in patients with pericarditis but is needed to rule out pericardial tamponade and pericardial constriction

Laboratory findings

- Elevation of inflammatory markers may support the diagnosis of pericarditis but are not considered to be a part of the diagnostic criteria.
- CBC: leukocytosis, ↑ ESR, ↑ CRP
- † Troponin I : suggest some degree of myocarditis.
- ↑ Creatinine kinase



ECG showing pericarditis. Note the widespread nature of the ST elevation and the PR depression

Diagnosis

ESC guidelines defined the diagnosis of acute pericarditis as 2 out of 4 of the following:

- 1) pericarditic chest pain:
- 2) pericardial rub;
- 3) new widespread ST-elevation or PR depression; and
- 4) pericardial effusion (new or worsening).
- Rule out other causes of acute chest pain (e.g., myocardial infarction, myocarditis) before making a diagnosis of acute pericarditis.

Treatment

- Pain management (analgesia, observation)
 - ⇒ NSAID therapy (Aspirin, Ibuprofen)
 - ⇒ Post-myocardial infarction pericarditis: avoid NSAIDs other than aspirin.
 - ⇒ Colchicine (in combination with NSAIDs or as a monotherapy). Useful both in acute episode and to prevent recurrence of pericarditis.
- Only consider prednisone in:
 - ⇒ severe cases (not responded to NSAID and Colchicine)
 - ⇒ or in pericarditis caused by uremia, connective tissue disease, or autoreactivity.
- Treat any known underlying causes
- Pericardectomy is only indicated for recurrent pericarditis once medical interventions have failed
- Treatment duration: until symptoms have resolved and CRP has normalized, but normally it is for 1-2 weeks duration.
- Reduce physical activity

Prognosis

- Recurrence
 - ⇒ Between 15 and 30% of patients with idiopathic acute pericarditis may have recurrent attacks, and this is considered to be an autoimmune phenomenon.
- Poor prognostic factors include:
 - ⇒ Temperature above 38°C
 - ⇒ Subacute disease course
 - ⇒ Presence of a large effusion or tamponade
 - ⇒ Unsuccessful therapy with nonsteroidal anti-inflammatory agents
- Factors associated with complicated pericarditis include:
 - ⇒ Early administration of high-dose corticosteroids
 - ⇒ Lack of colchicine treatment
 - ⇒ Elevated levels of high-sensitivity C-reactive protein

Acute pericarditis

- Symptoms include sharp, severe retrosternal chest pain worse with inspiration and a supine position.
- The classic physical finding is a pericardial friction rub. A low-grade fever is often
 present.
- **Diagnostic signs** include new widespread diffuse concave upwards ST elevation and/or PR depression on ECG and new or worsening pericardial effusion on echocardiography; blood tests generally suggest systemic inflammation.
- **Treatment:** All patients should be given a non-steroidal anti-inflammatory drug as first-line treatment. Colchicine should also be given unless the patient has tuberculous pericarditis.
- Complications include chronic recurrent pericarditis, cardiac tamponade, and constrictive pericarditis.

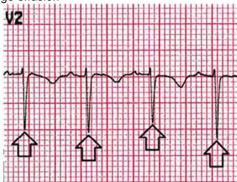
Pericardial effusion

Causes

- infectious pericarditis: viral, tuberculosis, pyogenic spread from septicaemia and pneumonia
- uraemia
- idiopathic
- post myocardial infarction (including Dressler's syndrome)
- malignancy
- heart failure
- · nephrotic syndrome
- hypothyroidism
- trauma
 - ⇒ CT is the most appropriate investigation
 - provide more information than Echo
 - quicker to obtain than (MRI).

Investigations

- ECG of pericardial effusion
 - ⇒ ECG reveals electrical alternans, which is caused by a "swinging" movement of the heart in a large effusion



Constrictive pericarditis

The right sided failure, ascites and pericardial calcification on x ray suggest a diagnosis of constrictive pericarditis.

Pathophysiology

Inflammation of the pericardium → fibrosis and constriction

Risk factors

- previous cardiac surgery
- · previous pericarditis,
- radiotherapy
- · connective tissue disease

Causes

- · Mediastinal irradiation
- TB:Tuberculous pericarditis is the commonest cause of constrictive pericarditis worldwide.
- any cause of purulent pericarditis

Features

- dyspnoea
- right heart failure: elevated JVP, ascites, oedema, hepatomegaly
- JVP shows prominent x and y descent
- pericardial knock loud S3
- Kussmaul's sign is positive (rise in JVP on inspiration)

Investigations

- CXR
 - ⇒ pericardial calcification
 - ⇒ can detect effusions only if larger than 250 mL.
- Echocardiography
 - ⇒ Indication → to assess for pericardial effusion and cardiac tamponade
 - ⇒ the best diagnostic tool for diagnosing pericardial effusion.
 - ⇒ shows <u>no increase</u> in the venous return with inspiration.

The key differences between constrictive pericarditis and cardiac tamponade are summarized in the table below:

	Cardiac tamponade	Constrictive pericarditis
JVP	Absent Y descent	X + Y present
Pulsus paradoxus	Present	Absent
Kussmaul's sign*	Rare	Present
Characteristic features		Pericardial calcification on CXR

- Kussmaul's sign* → a paradoxical rise in jugular venous pressure (JVP) on inspiration
- Kussmaul's sign (a rise in the JVP on inspiration) is more likely to be seen in constrictive pericarditis than cardiac tamponade.

Treatment

The first line of treatment of symptomatic constrictive pericarditis is pericardiotomy.

Cardiac tamponade

Cardiac tamponade is characterised by **Beck's triad** of:

- hypotension
- · raised JVP (with absent Y descent), and
- muffled heart sounds.

Definition

 an accumulation of pericardial fluid under pressure, leading to impaired cardiac filling and hemodynamic compromise

Features

- dvspnoea
- raised JVP, with an absent Y descent this is due to the limited right ventricular filling
- tachycardia
- Hypotension
 - the best clinical features that distinguishes cardiac tamponade from constrictive pericarditis

- hypotension is a late feature in constrictive pericarditis.
- muffled heart sounds
- pulsus paradoxus
 - ⇒ an exaggerated inspiratory decrease in systolic blood pressure
- Kussmaul's sign
 - ⇒ Rare
 - ⇒ Most common in constrictive pericarditis
- impalpable apex beat

Investigations

- ECG:
 - ⇒ tachycardia.
 - ⇒ low voltage,
 - ⇒ <u>electrical alternans</u>, (due to the <u>swinging movement</u> of the heart).
 - beat-to-beat variation in QRS-axis and amplitude.
- chest x-ray (enlarged cardiac silhouette with clear lung fields),
- echocardiogram (<u>chamber collapses</u>, abnormal venous flows, exaggerated respiratory variation of cardiac and venous flows).

Treatment

pericardiocentesis.

Hypotension is the best clinical features that distinguishes cardiac tamponade from constrictive pericarditis

⇒ hypotension is a <u>late</u> feature in constrictive pericarditis.

Hypertension (NICE guidelines 2019)

Definition

 Essential hypertension is defined as blood pressure (BP) ≥140/90 mmHg, with no secondary cause identified.

Causes

- Essential hypertension (95% of patients)
 - ⇒ No specific cause known. Multifactorial etiology including genetic and environmental factors
- Secondary hypertension (5% of patients)
 - ➡ RECENT: Renal (e.g., renal artery stenosis, glomerulonephritis), Endocrine (e.g., Cushing syndrome, hyperthyroidism, Conn syndrome), Coarctation of the aorta, Estrogen (oral contraceptives), Neurologic (raised intracranial pressure, psychostimulants use), Treatment (e.g., glucocorticoids, NSAIDs) are the causes of secondary hypertension.

When a question says: 'What is the most likely diagnosis?' think about what is epidemiologically the most common cause of hypertension? Therefore the answer is essential hypertension. The most likely cause of hypertension in an obese is still essential hypertension.

Diagnosis

Hypertension - NICE now recommend ambulatory blood pressure monitoring to aid diagnosis

Confirm diagnosis of hypertension in people with a: clinic blood pressure of 140/90 mmHg or higher and ABPM daytime average or HBPM average of 135/85 mmHg or higher.

Measuring blood pressure

 Palpate the radial or brachial pulse before measuring blood pressure with automated devices. If pulse irregularity is present, measure BP manually using direct auscultation over the brachial artery, because automated devices may not measure BP accurately if there is pulse irregularity (for example, due to atrial fibrillation).

Measure BP in both arms

- ⇒ If the difference between arms > 15 mmHg ⇒ repeat BP . If the difference remains > 15 mmHg:
 - Subsequent BP should be recorded from the arm with the higher reading.
 - Look for cases of unequal BP from the arms, e.g. supravalvular aortic stenosis.
- If BP in the clinic ≥ 140/90 mmHg:
 - ⇒ Take a second measurement during the consultation.
 - ⇒ If the second measurement is substantially different from the first, take a third measurement.
 - ⇒ Record **the lower** of the last 2 measurements as the clinic blood pressure.
- If **clinic BP** is between 140/90 mmHg and 180/120 mmHg, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. If ABPM is unsuitable or not tolerated, offer home blood pressure monitoring (HBPM).
- In people with symptoms of postural hypotension (falls or postural dizziness):
 - ⇒ measure BP with the person either supine or seated and with the person standing for at least 1 minute before measurement.
 - ⇒ If the systolic BP falls by 20 mmHg or more when the person is standing:
 - review medication
 - measure subsequent BP with the person standing
 - consider referral to specialist care if symptoms of postural hypotension persist.

Ambulatory blood pressure monitoring (ABPM)

- ⇒ The use of ambulatory blood pressure monitoring (ABPM) aims to:
 - prevent diagnosing 'white coat hypertension' as having hypertension in patients whose blood pressure climbs 20 mmHg whenever they enter a clinical setting.
 - ABPM has been shown to be a more accurate predictor of cardiovascular events than clinic readings.
- ⇒ at least 2 measurements per hour during the person's usual waking hours (for example, between 08:00 and 22:00)
- ⇒ use the average value of at least 14 measurements
- ⇒ If ABPM is not tolerated or declined HBPM should be offered.

Home blood pressure monitoring (HBPM)

- ⇒ for each BP recording, two consecutive measurements need to be taken, at least 1 minute apart and with the person seated
- ⇒ BP should be recorded twice daily, ideally in the morning and evening
- ⇒ BP should be recorded for at least 4 days, ideally for 7 days
- ⇒ discard the measurements taken on the first day and use the average value of all the remaining measurements.

Hypertension terms used in NICE guidelines 2019

Term	Definition	
Hypertension	clinic BP of ≥140/90 mmHg or higher and ABPM daytime average or HBPM average of ≥135/85 mmHg.	
White-coat hypertension	A discrepancy of more than 20/10 mmHg between clinic and average daytime ABPM or average HBPM measurements at the time of diagnosis.	
Masked hypertension	Clinic BP measurements are normal (<140/90 mmHg), but higher when taken outside the clinic using average daytime ABPM or average HBPM BP measurements.	
Persistent hypertension	High blood pressure at repeated clinical encounters.	
severe hypertension	Stage 3 hypertension: Clinic systolic BP ≥ 180 mmHg or clinic diastolic BP ≥ 120 mmHg.	
Accelerated hypertension (malignant hypertension)	A severe increase in BP to ≥180/120 mmHg (and often over 220/120 mmHg) with signs of retinal haemorrhage and/or papilloedema (swelling of the optic nerve). It is usually associated with new or progressive target organ damage and is also known as malignant hypertension.	

Hypertension Stages (NICE guidelines 2019)

Stage	Criteria	
Stage 1 hypertension	Clinic BP ≥ 140/90 mmHg and subsequent ABPM daytime average or HBPM average BP ≥ 135/85 mmHg	
Stage 2 hypertension	Clinic BP ≥ 160/100 mmHg and subsequent ABPM daytime average or HBPM average BP ≥ 150/95 mmHg	
Stage 3 or severe hypertension	Clinic systolic BP ≥ 180 mmHg, or clinic diastolic BP ≥ 120 mmHg	

Management (NICE guidelines 2019)

Non-pharmacological management

- Lifestyle advice is the **first line** in hypertension management
 - weight reduction: Of all the lifestyle modifications, weight reduction produces the greatest reduction in BP (A 10 kg weight loss is expected to decrease BP by 15–20 mmHg)
 - ⇒ **low salt diet**, aiming for less than 6g/day, ideally 3g/day. (reducing salt intake by 6g/day can lower systolic blood pressure by 10mmHg)
 - ⇒ low caffeine intake.

- ⇒ stop smoking, drink less alcohol
 - If a patient on antihypertensive and drink alcohol → Reduction of alcohol intake is the next step in treatment.

Starting antihypertensive drug treatment

- · any age with persistent stage 2 hypertension.
- age < 60 years with stage 1 hypertension and an estimated 10-year cardiovascular risk below 10%.
- age < 80 years with stage 1 hypertension who have 1 or more of the following:
 - ⇒ target organ damage
 - ⇒ established cardiovascular disease
 - ⇒ renal disease

 - ⇒ an estimated 10-year risk of cardiovascular disease of 10% or more.
- age > 80 years with stage 1 hypertension if their clinic BP >150/90 mmHg
- For patients < 40 years → consider specialist referral to exclude secondary causes.

Pharmacological management: Steps of hypertension treatment

Step 1 treatment

- ⇒ Age ≤ 55 OR any age, with T2DM with no black African origin → ACEi or ARB
- ⇒ Age ≤ 55 OR any age, with T2DM with black African origin → ARB
- ⇒ Age ≥ 55 without T2DM → CCB
- ⇒ black African origin of any age without T2DM → CCB
- ⇒ With heart failure → thiazide-like diuretic, such as indapamide in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.

Step 2 treatment

- ⇒ If BP not controlled on ACEi or ARB → Add CCB or thiazide-like diuretic.
- ⇒ If BP not controlled on CCB → Add ACEi or ARB or thiazide-like diuretic.
- ⇒ If BP not controlled on CCB in a black African → Add ARB (in preference to an ACEi)

Step 3 treatment

⇒ If BP not controlled with step 2 treatment → ACEi or ARB and CCB and thiazide-like diuretic.

Step 4 treatment

- ⇒ BP not controlled with the optimal tolerated doses of ACEi **or** ARB **and** CCB **and** thiazide-like diuretic → Resistant hypertension
- ⇒ Before considering further treatment for a person with resistant hypertension:
 - Confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings.
 - 2. Assess for postural hypotension.
 - 3. Discuss adherence
- ⇒ Confirmed resistant hypertension:
 - blood potassium ≤ 4.5 mmol/l → further diuretic therapy with low-dose spironolactone
 - monitor blood sodium and potassium and renal function within 1 month of starting treatment and repeat as needed thereafter.
 - blood potassium > 4.5 mmol/l → alpha-blocker or beta-blocker

Calcium channel blockers are now preferred to thiazides in the treatment of hypertension

Hypertension in diabetics - ACE-inhibitors are first-line regardless of age

ACE inhibitors have reduced efficacy in black patients and are therefore not used first-line

Drug choice

- hypertensive with benign prostatic hyperplasia → alpha-blockers
- hypertensive with heart failure or angina → beta-blockers
- hypertensive post myocardial infarction either a beta blocker or ACE inhibitor would be the agent of choice.
- calcium channel blockers are now considered superior to thiazides
- bendroflumethiazide is no longer the thiazide of choice

Use of multiple anti-hypertensives at low doses is preferable to having fewer tablets at higher doses, in view of the synergistic effectiveness of targeting several mechanisms of hypertension.

Blood pressure targets

Blood pressure target (based on clinic readings) for patients < 80 years - 140/90 mmHg

	Clinic BP	ABPM / HBPM
Age < 80 years	140/90 mmHg	135/85 mmHg
Age > 80 years	150/90 mmHg	145/85 mmHg

Recommendations for BP target

 British Hypertension Society Guidelines for Hypertension Management (BHS-IV) recommend a goal BP of less than 130/80 mmHg for patients with diabetes, renal impairment and established cardiovascular disease;

Hypertensive emergency

Definition

Hypertensive emergency: systolic BP ≥ 180 or diastolic BP ≥ 110 + end organ damage

Presentation

- The most common clinical presentations of hypertensive emergencies are:
 - ⇒ cerebral infarction (24.5%)
 - ⇒ pulmonary edema (22.5%),
 - ⇒ hypertensive encephalopathy (16.3%),
 - ⇒ congestive heart failure (12%).
 - ⇒ Other presentations include intracranial hemorrhage, aortic dissection, and eclampsia as well as acute myocardial infarction.

Management

Labetalol has both alpha- and beta-adrenoreceptor antagonistic activity and is <u>the first choice for hypertensive crises</u> where the aetiology is initially unclear.

- Gradual blood pressure lowering over the first 24 hours
 - \Rightarrow in the first hour : reduce mean arterial pressure (MAP) by 10 20 %
 - ⇒ in the next 23 hours: 5% to 15%, so that the final BP is reduced by 25% compared with baseline.
- IV antihypertensive : e.g. Labetolol
 - ⇒ The major risk of any oral agent used for hypertensive emergencies is ischaemic symptoms (for example myocardial infarction, angina pectoris or stroke) due to an excessive and uncontrolled hypotensive response usually due to lowering of BP to below the autoregulatory threshold. Therefore the use of oral agents should generally be avoided in the treatment of hypertensive emergencies if parenteral drugs are available.
- The exceptions to gradual BP lowering over the first 24 hours are:
 - ⇒ Acute ischemic stroke The BP should not lowered unless it is ≥185/110 mmHg in patients who are candidates for reperfusion therapy or ≥220/120 mmHg in patients who are not candidates for reperfusion therapy.
 - ⇒ Acute aortic dissection The systolic BP should rapidly lowered to a target of 100 to 120 mmHg (to be attained in 20 minutes).
 - ⇒ Spontaneous hemorrhagic stroke The systolic BP can be rapidly reduced if no contraindications exist.

MAP = diastolic blood pressure + [(systolic blood pressure - diastolic blood pressure)/3]
Or MAP = (2x diastolic + systolic)/3

Parenteral drugs for treatment of hypertensive emergencies

	Side effects (SE)	Notes
Labetalol (Adrenergic inhibitor) Beta-Blocker With Alpha-Blocking Activity	Nausea/vomiting, paresthesias (eg, scalp tingling), bronchospasm, dizziness, nausea, heart block	Avoid in acute decompensated heart failure. Use cautiously in obstructive or reactive airway. Beta-blocker should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.
Nitroglycerin (glyceryl trinitrate) (Vasodilators)	Hypoxemia, tachycardia (reflex sympathetic activation), headache, vomiting, flushing, methemoglobinemia, tolerance with prolonged use	used as adjunctive therapy for patients with acute coronary syndrome or acute pulmonary edema. contraindicated in patients with increased intracranial pressure (eg, intracranial hemorrhage)
Nicardipine (Vasodilators) Calcium Channel Blocker, Dihydropyridine	Tachycardia, headache, dizziness, nausea, flushing, local phlebitis, edema	Avoid use in acute heart failure. Caution with coronary ischemia.
Clevidipine (Vasodilators) Calcium Channel Blocker, Dihydropyridine	Atrial fibrillation (most common SE), nausea, lipid formulation contains potential allergens (eg, soy, egg)	Avoid in patients with defective lipid metabolism (hypertriglyceridemia is an expected SE). Patients who develop hypertriglyceridemia (eg, >500 mg/dL) are at risk of developing pancreatitis. Dihydropyridine calcium channel blockers may cause negative inotropic effects and exacerbate HF.
Hydralazine (Vasodilators) Direct vasodilation of arterioles	Sudden precipitous drop in blood pressure, tachycardia, flushing, headache, vomiting, aggravation of angina	In general, hydralazine should be avoided due to its prolonged and unpredictable hypotensive effect. Contraindicated in coronary artery disease; mitral valve rheumatic heart disease and SLE.
Nitroprusside (Vasodilators)	Elevated intracranial pressure, decreased cerebral blood flow, reduced coronary blood flow in CAD, cyanide and thiocyanate toxicity, nausea, vomiting, muscle spasm, flushing, sweating	In general, nitroprusside should be avoided due to its toxicity. avoid in AMI, CAD, CVA, elevated intracranial pressure, renal or hepatic impairment.
Phentolamine (Adrenergic inhibitor) Alpha ₁ Blocker	Tachycardia, flushing, headache, nausea/vomiting	Alternative option for catecholamine excess (eg, adrenergic crisis secondary to pheochromocytoma or cocaine overdose).

Hypertensive urgency

Definition

Hypertensive urgency: systolic BP ≥ 180 or diastolic BP ≥ 110 + NO end organ damage

Presentation

- Asymptomatic patient with a BP in the "severe" range (ie, ≥180/≥120 mmHg)
- Often a mild headache, but **no** signs or symptoms of acute end-organ damage.

Management

- All patients should be provided a quiet room in which to rest. This may produce a fall in blood pressure ≥20/10 mmHg in approximately one-third of adults. If this is not effective, antihypertensive drugs may be given.
- Gradual lowering of the BP over a period of hours to days to <160/<100 mmHg or no more than 25 to 30% of baseline BP.
- The risk of adverse events (eg, stroke or myocardial infarction) that may occur if the BP is lowered too rapidly or to a level below the ability for autoregulation to maintain adequate tissue perfusion.
- Can often be safely managed in the clinician's office
- Add or modify oral antihypertensive

Malignant hypertension (Accelerated hypertension)

A patient with malignant hypertension always has retinal papilledema

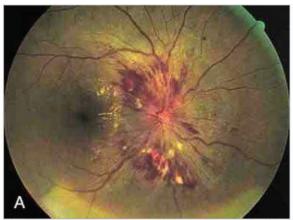
Definition

- BP ≥180/120 mmHg (often over 220/120 mmHg) with signs of retinal haemorrhage and/or papilloedema (swelling of the optic nerve).
- It is usually associated with new or progressive target organ damage

Pathophysiology

 The pathologic hallmark of malignant hypertension is <u>fibrinoid necrosis of the</u> arterioles which occurs systemically, but specifically in the kidneys.

Management: as hypertensive emergency



Papilledema. Note the swelling of the optic disc, with blurred margins

Secondary hypertension

General indicators of secondary hypertension

- Young age (< 40 years) at onset of hypertension
- Onset of diastolic hypertension at an older age (> 55 years)
- Abrupt onset of hypertension
- End-organ damage that is disproportionate to the degree of hypertension
- Recurrent hypertensive crises
- Resistant hypertension: hypertension that is resistant to treatment with at least three antihypertensives of different classes including a diuretic

Causes

- Primary hyperaldosteronism, including Conn's syndrome (5-10% of hypertensive patients)
 - ⇒ the single most common cause of secondary hypertension
 - ⇒ ↑BP + ↓ K⁺ + ↑ Aldosterone
 - ⇒ CT or MRI of the abdomen identifies a secretory adrenal adenoma
- Renal diseases: include
 - ⇒ glomerulonephritis
 - ⇒ pyelonephritis
 - ⇒ Reflux-associated scarring is the commonest renal disease.
 - This will cause abnormalities on dimercaptosuccinic acid (DMSA) scan.
 - ⇒ adult polycystic kidney disease
 - ⇒ renal artery stenosis
- Coarctation of the aorta (the commonest non-renal cause)
- Endocrine disorders (other than primary hyperaldosteronism):
 - ⇒ phaeochromocytoma
 - ⇒ Cushing's syndrome
 - \Rightarrow Liddle's syndrome \Rightarrow (\uparrow BP + \downarrow K⁺ + \uparrow Na⁺)
 - hypokalaemic hypertension
 - metabolic alkalosis
 - low plasma renin and aldosterone (called pseudo-hyperaldosteronism).

- ⇒ congenital adrenal hyperplasia (11-beta hydroxylase deficiency)
- ⇒ acromegaly
- · Fibromuscular dysplasia,
 - ⇒ a rare cause of hypertension and hypokalaemia,
 - ⇒ more common in women.
 - ⇒ It causes hyperreninaemic hyperaldosteronism.
- Pregnancy (PIH, pre-eclampsia, eclampsia)
- Drugs
 - ⇒ Liquorice ingestion
 - causes a primary aldosterone type picture.
 - It is caused by glycyrrhizic acid contained in liquorice, blocking the enzyme 11b hydroxysteroid dehydrogenase. This prevents the inactivation of cortisol, which in turn activates mineralocorticoid receptors in the kidney. driving hypokalaemic metabolic alkalosis with hypertension.
 - ⇒ NSAIDs, combined oral contraceptive pill, steroids, MAOI

Different diagnostics for causes of secondary hypertension			
Diagnostic findings	Underlying condition		
Hypokalaemia	Conn syndromeRenal artery stenosis		
Metabolic alkalosis and ↑ aldosterone-to-renin ratio	Conn syndrome		
Difference in blood pressure in both arms	Takayasu arteritisAortic dissectionAortic arch syndromeSubclavian steal syndrome		
Of upper and lower limbs	Coarctation of the aorta distal to the left subclavian artery		
 Daytime sleepiness (Epworth scale, Berlin questionnaire) Nondipping in 24-hour blood pressure monitoring (the failure of BP to fall by ≥10% during sleep.) 	Obstructive sleep apnoea		
 Increased 24-hour urinary metanephrines ↑ Serum calcium, ↑ PTH level, ↓ serum 	Pheochromocytoma Hyperparathyroidism		
phosphates	, p 5. p 5. 5. 5. 5. 5. 5. 6. 6. 6. 6.		
↑ Serum cortisol	 Excess of glucocorticoids (e.g., Cushing syndrome) 		
■ ↓TSH, ↑ free T4	 Hyperthyroidism 		

MRCPUK- part 2- March 2017: A 28-year-old woman of Afro-Caribbean ethnic origin c/o difficult-to-manage hypertension, despite taking maximal-dose amlodipine and indapamide. The GP trialled an ACE inhibitor, but this was discontinued due to a rise in serum creatinine. Renin and aldosterone are both Elevated. K is 3.1 mmol. Which of the following is the most likely diagnosis?

- ➡ Fibromuscular renal artery dysplasia
 - This patient's age and ethnicity suggest that her hypertension is related to fibromuscular dysplasia rather than to atherosclerotic renal artery stenosis.
 - The renin and aldosterone elevation, coupled with hypokalaemia and deterioration in renal function on starting ACE inhibitors, are consistent with the diagnosis.

Differences in blood pressure between arms:

- Up to 10 mmHg difference → Normal variant (physiological)
- Difference > 10 mmHg: → abnormal:
 - ⇒ + radio-radial or radio-femoral delay (NO Leg claudication) → proximal coarctation of the aorta (involves the left subclavian artery origin)
 - → + arm claudication, intermittent vertigo, ataxia or diplopia, or facial sensory symptoms (NO Leg claudication) → Subclavian steal syndrome

 | Subclavian |
 - → + Leg claudication (chronic intermittent leg pain, exacerbated by exercise and relieved by rest) → Peripheral vascular disease

Hypokalaemia and hypertension

Liddle's syndrome: hypokalaemia + hypertension

Hypokalaemia with hypertension	Hypokalaemia without hypertension
 Cushing's syndrome Conn's syndrome (primary hyperaldosteronism) Liddle's syndrome (autosomal dominant disorder that mimics hyperaldosteronism) renal artery stenosis 11-beta hydroxylase deficiency ≥ 21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension Carbenoxolone, an anti-ulcer drug, and liquorice excess 	 ■ Diuretics ■ GI loss (e.g. Diarrhoea, vomiting) ■ renal tubular acidosis (type 1 and 2) ⇒ type 4 renal tubular acidosis is associated with hyperkalaemia. ■ Bartter's syndrome ■ Gitelman syndrome

- The first step in case of (↑ BP + ↓ K+) should be further simple investigations → Plasma renin and aldosterone levels
 - ⇒ Cushing's & Conn's → high aldosterone and a low renin,
 - ⇒ Renal artery stenosis → high renin and aldosterone
 - ⇒ Liddle's syndrome → low renin and aldosterone.

Hypertension in pregnancy

Labetalol is first-line for pregnancy-induced hypertension

Physiology

- The blood pressure in normal pregnancy:
 - ⇒ usually falls in the first trimester (particularly the diastolic), and continues to fall until
 20-24 weeks
 - ⇒ after this time the blood pressure usually increases to pre-pregnancy levels by term

Definition

- Hypertension in pregnancy in usually defined as:
 - ⇒ systolic > 140 mmHg or diastolic > 90 mmHg
 - ⇒ or an increase above booking readings of > 30 mmHg systolic or > 15 mmHg diastolic

Classification

Pre-existing hypertension	Pregnancy-induced hypertension (PIH, also known as gestational hypertension)	Pre-eclampsia
A history of hypertension before pregnancy or BP > 140/90 mmHg before 20 weeks gestation	Hypertension (as defined above) occurring in the second half of pregnancy (i.e. after 20 weeks)	Pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours)
No proteinuria, no oedema	No proteinuria, no oedema	Oedema may occur but is now less commonly used as a criterion
Occurs in 3-5% of pregnancies and is more common in older women	Occurs in around 5-7% of pregnancies	Occurs in around 5% of pregnancies
	Resolves following birth (typically after one month). Women with PIH are at increased risk of future pre-eclampsia or hypertension later in life	

Treatment of chronic hypertension with pregnancy

- Pre-pregnancy advice: If they are taking ACE inhibitors or ARBs, thiazide or thiazide-like
 diuretics and planning for pregnancy discuss an alternative antihypertensive treatment, stop
 it if they become pregnant, the limited evidence available has not shown an increased risk
 of congenital malformation with any other antihypertensive.
- Best antihypertensive:
 - ⇒ 1st line : labetalol
 - ⇒ 2nd line: nifedipine (if labetalol is not suitable)
 - ⇒ 3rd line: methyldopa (if both labetalol and nifedipine are not suitable)
- Target BP: 135/85 mmHg
- Aspirin 75–150 mg once daily from 12 weeks.
- Offer placental growth factor (PIGF)-based testing to help rule out pre-eclampsia between 20 weeks and up to 35 weeks of pregnancy, if women with chronic hypertension or PIH are suspected of developing pre-eclampsia.

Treatment of hypertension in the postnatal period

- If women not planning to breastfeed → treat as hypertension in general
- If women planning to breastfeed:
 - ⇒ 1st line:
 - non-black African or Caribbean women: enalapril
 - black African or Caribbean women: nifedipine or amlodipine if the woman has previously used this to successfully control her BP.
 - ⇒ 2nd line: combination of nifedipine (or amlodipine) and enalapril
 - ⇒ 3rd line: add atenolol or labetalol to the combination treatment **or** swapping 1 of the medicines already being used for atenolol or labetalol.
- avoid using diuretics or angiotensin receptor blockers for women who are breastfeeding.

Treatment of hypertension in the postnatal period (NICE guidelines June 2019)

- If women not planning to breastfeed → treat as hypertension in general
- If women planning to breastfeed:
 - ⇒ 1st line:
 - non-black African or Caribbean women: enalapril
 - black African or Caribbean women: nifedipine or amlodipine if the woman has previously used this to successfully control her BP.
 - ⇒ 2nd line: combination of nifedipine (or amlodipine) and enalapril
 - 3rd line: add atenolol or labetalol to the combination treatment or swapping 1 of the medicines already being used for atenolol or labetalol.
- Avoid using diuretics or angiotensin receptor blockers for women who are breastfeeding.

Pre-eclampsia/Eclampsia

Severe pre-eclampsia - restrict fluids

Eclampsia - give magnesium sulphate first-line

Definitions

- Pre-eclampsia: is a condition seen after 20 weeks gestation characterised by pregnancyinduced hypertension in association with proteinuria.
 - ⇒ use albumin: creatinine ratio (8 mg/mmol) **or** protein: creatinine ratio (≥30 mg/mmol) to confirm significant proteinuria (Do not use 24-hour proteinuria or first morning urine void).
- Eclampsia: development of seizures in association pre-eclampsia.

Risk factors

- > 40 years old
- nulliparity (or new partner)
- multiple pregnancybody mass index > 30 kg/m^2
- · diabetes mellitus
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- · previous history of pre-eclampsia
- pre-existing vascular disease such as hypertension or renal disease
- There is some evidence to suggest that pre-eclampsia is actually less common in smokers

Features of pre-eclampsia

- severe headache
- problems with vision, such as blurring or flashing before the eyes
- severe pain just below the ribs
- sudden swelling of the face, hands or feet.

Prevention of pre-eclampsia

- Aspirin 75–150 mg of aspirin daily from 12 weeks until the birth of the baby is indicated for pregnant with:
 - Doe of the following high risk factor for pre-eclampsia:
 - hypertensive disease during previous pregnancies
 - chronic kidnev disease
 - autoimmune disorders such as SLE or antiphospholipid syndrome
 - type 1 or 2 diabetes mellitus
 - chronic hypertension.
 - ⇒ More than one of the following moderate risk factor for pre-eclampsia:
 - first pregnancy
 - age 40 years or older

- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m2 or more at first visit
- family history of pre-eclampsia
- multi-fetal pregnancy.

Treatment

- · Pre-eclampsia
 - ⇒ Target blood pressure: BP of 135/85 mmHg or less
 - ⇒ Best antihypertensive:
 - 1st line : labetalol
 - 2nd line: nifedipine (if labetalol is not suitable)
 - 3rd line: methyldopa (if both labetalol and nifedipine are not suitable)
 - Consider magnesium sulfate treatment, if 1 or more of the following features of severe pre-eclampsia is present:
 - ongoing or recurring severe headaches
 - visual scotomata
 - nausea or vomiting
 - epigastric pain
 - oliguria and severe hypertension
 - progressive deterioration in laboratory blood tests (such as rising creatinine or liver transaminases or falling platelet count).

Eclampsia

- ⇒ Magnesium sulphate is used to both prevent seizures in patients with severe preeclampsia and treat seizures once they develop.
 - IV bolus of 4g over 5-15 minutes followed by an infusion of 1g / hour for 24 hours.
 - Recurrent fits should be treated with a further dose of 2–4 g given intravenously over 5 to 15 minutes.
 - urine output, reflexes, respiratory rate and oxygen saturations should be monitored during treatment
 - treatment should continue for 24 hours after last seizure or delivery (around 40% of seizures occur post-partum)
- Other important aspects of treating severe pre-eclampsia/eclampsia include fluid restriction to avoid the potentially serious consequences of fluid overload (limit maintenance fluids to 80 ml/hour)
- delivery of the baby is the most important and definitive management step. The timing depends on the individual clinical scenario.

Pulmonary arterial hypertension (PAH)

Definition

 Sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest or 30 mmHg after exercise.

Epidemiology

- More common in females
- · Typically presents at 20-40 years old

WHO Classification & causes

- 1. Group 1: idiopathic pulmonary arterial hypertension (IPAH)
 - ⇒ Idiopathic (previously termed primary pulmonary hypertension (PPH)
 - ⇒ 10% are familial (autosomal dominant)
 - ⇒ Diagnosed when no underlying cause can be found
 - ⇒ Endothelin thought to play a key role in pathogenesis

2. Group 2: Pulmonary hypertension with left heart disease

- ⇒ Congenital heart disease with systemic to pulmonary shunts
- ⇒ Left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation
- 3. Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
 - ⇒ COPD
 - ⇒ Interstitial lung disease
 - ⇒ Sleep apnoea
 - ⇒ High altitude
- 4. Group 4: Pulmonary hypertension due to thromboembolic disease
- 5. Group 5: Miscellaneous conditions
 - ⇒ Lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis
 - ⇒ Collagen vascular disease
 - ⇒ HIV (the mechanism by which HIV infection produces pulmonary hypertension remains unknown)
 - ⇒ Sickle cell disease
 - Haemoglobinopathies (eg: sickle cell anemia, thalassemia) intravascular hemolysis → ↓ nitric oxide (NO) → pulmonary vasoconstriction
 - ⇒ Drugs and toxins: cocaine and anorexigens (e.g. fenfluramine)

Increased pressure in pulmonary circuit → elevated right ventricular afterload → dilatation and/or hypertrophy of the right heart → right heart failure and arrhythmias

Lung disease can cause pulmonary hypertension by hypoxic vasoconstriction, whereas the heart can cause pulmonary hypertension by pump failure and subsequent fluid backup and stasis.

- Pulmonary arterial hypertension is caused by an intrinsic increase in the resistance of the pulmonary vasculature, while pulmonary hypertension can be caused by secondary aetiologies such as lung disease and heart failure.
- The most common cause of pulmonary arterial hypertension is idiopathic, while the most common overall cause of pulmonary hypertension is left-sided heart failure.

Features

Women with pulmonary hypertension should avoid becoming pregnant due to very high mortality levels

Bosentan - endothelin-1 receptor antagonist

- Symptoms
 - ⇒ exertional dyspnoea is the most frequent symptom
 - progressive SOB
 - ⇒ chest pain and syncope may also occur
- On examination:
 - ⇒ cyanosis
 - Nail clubbing
 - ⇒ raised JVP with prominent 'a' waves,
 - ⇒ left parasternal heave (due to right ventricular hypertrophy)
 - ⇒ loud P2
 - ⇒ tricuspid regurgitation

Investigation

- Doppler echocardiography
 - ⇒ the initial investigation of choice
 - the jet associated with tricuspid regurgitation can be visualised adequately (tricuspid regurgitant jet velocity)
- · Right heart catheterization
 - ⇒ confirmatory test
 - ⇒ the gold standard for the diagnosis

World Health Organization (WHO) functional classification for pulmonary hypertension

Class	WHO functional classification for pulmonary hypertension
I	No limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope.
II	Slight limitation of physical activity. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope. Comfortable at rest.
III	Marked limitation of physical activity. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope. Comfortable at rest
IV	Inability to carry on any physical activity without symptoms. Dyspnea and/or fatigue may be present even at rest.

Management

- Treatment of the underlying cause for example:
 - ⇒ Anticoagulants for PE
 - ⇒ Bronchodilators and inhalation corticosteroids for COPD,
 - ⇒ CPAP for patients with obstructive sleep apnea
- Acute vasodilator testing is central to deciding on the appropriate management strategy.

- Acute vasodilator testing aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide
 - If there is a positive response → oral calcium channel blockers
 - If there is a negative response:
 - prostacyclin analogues: treprostinil, iloprost
 - endothelin receptor antagonists: bosentan
 - phosphodiesterase inhibitors: sildenafil
- · Diuretics if right heart failure
- Heart-lung transplant

Whilst only 10-15% of patients appear to have a pulmonary vascular tree responsive to calcium antagonism, these agents still constitute the initial therapy of choice according to guidelines, but only in those patients who show a response to vasodilator testing.

Complication

Cor pulmonale

Angina pectoris

Non-atherosclerotic angina would be associated with conditions such as

- Thyrotoxicosis
- Aortic regurgitation
- · Aortic stenosis
- Hypertrophic cardiomyopathy
- Anaemia

Anginal pain is:

- 1. constricting discomfort in the front of the chest, or in the neck, shoulders, jaw, or arms
- 2. precipitated by physical exertion
- 3. relieved by rest or GTN within about 5 minutes.
- Three of the features above are defined as typical angina.
- Two of the three features above are defined as atypical angina.
- One or none of the features above are defined as **non-anginal chest pain**.

Features which make a diagnosis of stable angina unlikely are when the chest pain is:

- continuous or very prolonged and/or
- unrelated to activity and/or
- brought on by breathing in and/or
- associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing.
 Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain).

Investigations for stable chest pain

- First-line: 64-slice CT coronary angiography (CTCA)
- Second-line: non-invasive functional testing (if CTCA is non-diagnostic.)
 - ⇒ Myocardial perfusion scan (MPS) with single photon emission computed tomography (SPECT) (MPS with SPECT) or
 - ⇒ stress echocardiography or
 - ⇒ first-pass contrast-enhanced magnetic resonance perfusion or
 - ⇒ MRI for stress-induced wall motion abnormalities.
- **Third-line**: invasive coronary angiography (when the results of non-invasive functional imaging are inconclusive)

In the context of risk factors for ischaemic heart disease (hypertension, hypercholesterolaemia, smoking), the clinical diagnosis should be confirmed with non-invasive functional scanning such as myocardial perfusion scanning with SPECT.

- High-risk patients with classic angina symptoms should proceed directly to coronary angiography.
- Offer 64- slice (or above) CT coronary angiography if:
 - 1. clinical assessment indicates typical or atypical angina or
 - clinical assessment indicates non-anginal chest pain but 12- lead resting ECG has been done and indicates ST- T changes or Q waves.
- Low-risk patients can be evaluated with non-invasive stress imaging.
- Offer non-invasive functional imaging for myocardial ischaemia if 64-slice (or above) CT coronary angiography has shown CAD of uncertain functional significance or is nondiagnostic.
 - ⇒ non-invasive functional testing for myocardial ischaemia
 - myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT)
 - Use adenosine, dipyridamole or dobutamine as stress agents
 - 2. stress echocardiography
 - Use exercise or dobutamine for stress echocardiography or MR imaging for stress-induced wall motion abnormalities.
 - 3. first-pass contrast-enhanced magnetic resonance (MR) perfusion
 - use adenosine or dipyridamole as stress agents
 - 4. MR imaging for stress-induced wall motion abnormalities
 - ⇒ Take account of locally available technology and any contraindications (for example, disabilities, frailty, limited ability to exercise) when deciding on the imaging method.
- Offer invasive coronary angiography as a third-line investigation when the results of noninvasive functional imaging are inconclusive.
- Treadmill exercise is no longer recommended in the work-up of new-onset chest pain.

Definition of significant coronary artery disease (CAD)

- CT coronary angiography is:
 - ⇒ ≥ 70% diameter stenosis of at least one major epicardial artery segment or
 - ⇒ ≥ 50% diameter stenosis in the left main coronary artery

Factors intensifying ischaemia

- Such factors allow less severe lesions (for example, ≥ 50%) to produce angina:
 - ⇒ reduced oxygen delivery: anaemia, coronary spasm
 - ⇒ increased oxygen demand: tachycardia, left ventricular hypertrophy
 - ⇒ large mass of ischaemic myocardium: proximally located lesions
 - ⇒ longer lesion length.

Factors reducing ischaemia which may render severe lesions (≥ 70%) asymptomatic:

- · Well-developed collateral supply.
- Small mass of ischaemic myocardium: distally located lesions, old infarction in the territory of coronary supply.

ESC guidelines 2017

- A reduction in chest pain after nitroglycerin (glyceryl trinitrate) administration can be misleading and is not recommended as a diagnostic manoeuvre
- In cases of symptom relief after nitroglycerin administration, another 12-lead ECG must be obtained.
- A complete normalization of the ST-segment elevation after nitroglycerin administration, along with complete relief of symptoms, is suggestive of coronary spasm, with or without associated MI. In these cases, an early coronary angiography (within 24 h) is recommended.
- In cases of recurrent episodes of ST-segment elevation or chest pain, **immediate** angiography is required.

Drug management

A beta-blocker or a calcium channel blocker is used first-line to prevent angina attacks

You should still use bisoprolol in patients with COPD and IHD, because it carries an important outcome benefit

Prinzmetal angina - treatment = dihydropyridine calcium channel blocker

Medication

- all patients should receive aspirin and a statin in the absence of any contraindication
- sublingual glyceryl trinitrate to abort angina attacks
- NICE recommend using either a beta-blocker or a calcium channel blocker first-line based on 'comorbidities, contraindications and the person's preference'
- if a calcium channel blocker is used as monotherapy a rate-limiting one such as verapamil
 or diltiazem should be used. If used in combination with a beta-blocker then use a longacting dihydropyridine calcium-channel blocker (e.g. modified-release nifedipine).
 Remember that beta-blockers should not be prescribed concurrently with verapamil (risk of
 complete heart block)
- if there is a poor response to initial treatment then medication should be increased to the maximum tolerated dose (e.g. for atenolol 100mg od)
- if a patient is still symptomatic after monotherapy with a beta-blocker add a calcium channel blocker and vice versa
- if a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs:
 - ⇒ a long-acting nitrate.
 - ⇒ ivabradine,
 - ⇒ nicorandil or
 - ⇒ ranolazine

- if a patient is taking both a beta-blocker and a calcium-channel blocker then only add a third drug whilst a patient is awaiting assessment for PCI or CABG
- The FREEDOM trial demonstrated that in diabetic patients CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction.
- Cardioselective calcium antagonists such as verapamil and diltiazem do not affect prognosis in angina although they may impact on symptoms by reducing heart rate.
- If a patients don't tolerate beta-blockade, ivabradine may be a more appropriate intervention.

Nitrate tolerance

- many patients who take nitrates develop tolerance and experience reduced efficacy
- the BNF advises that patients who develop tolerance should take the second dose of isosorbide mononitrate after 8 hours, rather than after 12 hours. This allows blood-nitrate levels to fall for 4 hours and maintains effectiveness
- this effect is not seen in patients who take modified release isosorbide mononitrate
- the explanation for nitrate tolerance → generation of reactive oxygen species
 - ⇔ chronic nitrate therapy → ↑vascular oxidative stress → ↑ degradation of nitric oxide
 (NO) → reduced bioavailability

Ivabradine

- action
 - ⇒ (I_f ('funny' ion) channel inhibitor which is highly expressed in the sinoatrial node)
 → reducing the heart rate
- Indications
 - ⇒ a new class of anti-anginal drug
 - there is no evidence currently of superiority over existing treatments of stable angina
 - ⇒ heart failure:
 - with (NYHA) class II–IV stable chronic heart failure with systolic dysfunction and who are in sinus rhythm with a heart rate of 75 bpm or more and who are given ivabradine in combination with standard therapy including β-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when β-blocker therapy is contraindicated or not tolerated and with a left ventricular ejection fraction of 35% or less.
- · adverse effects:
 - ⇒ visual effects, particular **luminous phenomena**, are common.
 - sensations of enhanced brightness in a fully maintained visual field
 - due to blockage of I_h ion channels in the retina, which are very similar to cardiac I_h
 - mild, transient, and fully reversible.
 - ⇒ Bradycardia, due to the mechanism of action,

Ulceration of an atheromatous plaque of the abdominal aorta is the most common source of emboli in old man presented with acute pain, pallor and absent pulses in his leg.

MRCPUK-part-1-January 2018 exam: Which cell type is most implicated in the development of coronary artery plaques?

Macrophages

Coronary artery bypass graft (CABG)

- There are two main approaches.
 - 1. In one, the left internal thoracic artery (internal mammary artery) is diverted to the left anterior descending branch of the left coronary artery.
 - In the other, a great saphenous vein is removed from a leg; one end is attached to the aorta or one of its major branches, and the other end is attached to the obstructed artery.
- CABG is superior to PCI in multivessel coronary disease.
- indicated when coronary arteries have a 50% to 99% obstruction.
- CABG guidelines state CABG is the preferred treatment for:
 - ⇒ Disease of the left main coronary artery (LMCA).
 - ⇒ Disease of all three coronary arteries (LAD, LCX and RCA).
 - ⇒ Diffuse disease not amenable to treatment with a PCI.
 - ⇒ high-risk patients such as those with severe ventricular dysfunction (i.e. low ejection fraction), or diabetes mellitus.

Benefits

- ⇒ relief of angina
- ⇒ no survival benefit with bypass surgery vs. medical therapy in stable angina
- ⇒ Bypass surgery does not prevent future myocardial infarctions.
- Complications
 - ⇒ The incidence of acute coronary syndrome within 30 days of CABG is high, at around 17.5%.
 - ⇒ Aneurysms are a rare and late complication of CABG.

Cardiac syndrome X

- · consist of:
 - ⇒ angina-like chest pain during exertion
 - ⇒ characteristic ECG changes during exercise testing
 - ⇒ normal coronary arteries on cardiac catheterisation
 - ⇒ no inducible coronary artery spasm during catheterisation

Acute coronary syndrome

Poor prognostic factors

- age
- · development (or history) of heart failure
- · peripheral vascular disease
- · reduced systolic blood pressure
- Killip class*
- initial serum creatinine concentration
- · elevated initial cardiac markers
- cardiac arrest on admission
- ST segment deviation

Clinical factors which are good indicators of ACS:

- typical pain lasting at least 15 minutes, associated nausea, and sweating.
- Response to GTN should not be used as indicator of ACS

ACS referral

Chest pain Referral guidelines:

- current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission
- chest pain 12-72 hours ago: refer to hospital the same-day for assessment
- chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

Myocardial infarction

DVLA advice post MI - cannot drive for 4 weeks

Inferior MI - right coronary artery lesion

- The most specific feature, which suggests that the pain is myocardial ischaemia, is the radiation to the jaw, which is relatively specific for pain of myocardial ischaemia.
- The clinical classification of MI includes: (NICE 2010)
 - ⇒ Type 1: ischaemia due to a primary coronary event such as plaque, fissuring or dissection.
 - ⇒ **Type 2**: ischaemia due to either increased oxygen demand or decreased supply, such as coronary spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.

The diurnal variation of myocardial ischaemia

- There is a diurnal variation in presentation of myocardial ischaemia.
- Which physiological process is responsible for this? → Vasospasm
- The peak incidence of **STEMI** and the peak incidence of death due to ischaemic heart disease both coincide at **around 8-9 am.**
 - ⇒ The early morning is associated with several physiological and haematological factors which predispose to vasospasm, infarction and death.
 - ⇒ There is
 - † adrenergic activity
 - †plasma fibrinogen levels
 - † inhibition of fibrinolysis and
 - † platelet adhesiveness.
- Interestingly, NSTEMIs are not associated with this degree of diurnal rhythm.
- Precipitating factors for an infarct include:
 - ⇒ physical exertion
 - ⇒ Rest , Sleep
 - ⇒ Surgical procedure
 - ⇒ Emotional stressors.

Risk factors

The **worst** risk factor for CAD is diabetes mellitus, but the most **common** risk is hypertension.

The highest prevalence of myocardial infarction is 72 hours post operation. Patients with diabetes may not have chest pain due to autonomic dysfunction.

Investigations

- ECG (best initial test)
- Cardiac troponin levels: Measure as soon as possible and repeat after 1-6 hours.
- Transthoracic echocardiography: if the diagnosis is unclear. Findings:
 - ⇒ Wall motion abnormalities
 - ⇒ Decreased LV function

Typical Electrocardiographic Evolution of a STEMI

EKG Abnormality	Onset	Disappearance
Hyperacute T waves (tall, peaked T waves in leads facing infarction)	Immediately	6–24 hours
ST-segment elevation	Immediately	1–6 weeks
Q waves longer than 0.04 seconds	One to several days	Years to never
T wave inversion	6–24 hours	Months to years

Myocardial infarction: management

Primary percutaneous coronary intervention is the gold-standard treatment for ST-elevation myocardial infarction

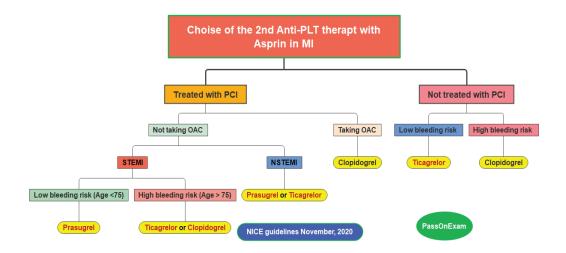
PCI: stent thrombosis - withdrawal of antiplatelets biggest risk factor

Clopidogrel inhibits ADP binding to platelet receptors

Ticagrelor has a similar mechanism of action to clopidogrel - inhibits ADP binding to platelet receptors

PCI - patients with drug-eluting stents require a longer duration of clopidogrel therapy

- Glyceryl trinitrate
 - ⇒ Sublingual glyceryl trinitrate and intravenous morphine + metoclopramide should be given to help relieve the symptoms.
 - ⇒ ongoing pain despite the use of sublingual GTN is suggestive of continuing myocardial ischaemia/infarction → IV GTN
 - · Aspirin 300mg.
 - **⇒** the initial drug therapy
 - ⇒ Aspirin 300mg should be given to all patients (unless contraindicated).
 - It is safe in the post-surgical patient with no signs of bleeding at three days post operation.
 - ⇒ A second antiplatelet is normally given, usually ticagrelor, clopidogrel or prasurgel (all are antagonists of the P2Y₁₂ adenosine diphosphate receptor).
 - (Aspirin + ticagrelor) is better than (aspirin + clopidogrel)
 - ticagrelor was associated with a 13% relative reduction in cardiovascular events versus a conventional clopidogrel based regimen.
 - This has driven use of ticagrelor in place of clopidogrel in major guidelines on antiplatelet therapy post STEMI.
 - A loading dose of 180 mg stat is recommended at the time of diagnosis of STEMI.
 - This was also associated with increased risk of bleeding events when compared to aspirin and clopidogrel.
 - ⇒ NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital. The dose of clopidogrel is 300 mg in ACS.
 - Other treatments that may be given include bivalirudin (a direct thrombin inhibitor, usually
 given alongside aspirin + clopidogrel) and a form of heparin (either low-molecular
 weight or unfractionated).
 - ⇒ Heparin in Non-STEMI (has no benefit in ST elevation MI).
 - do not routinely give oxygen, only give if sats < 94%*
 - *NICE suggest the following in terms of oxygen therapy:
 - do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
 - people with oxygen saturation (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
 - people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.
 - ⇒ ESC guidelines 2017 state that: routine oxygen is not recommended when SaO₂ is ≥ 90%.
 - perform an ECG as soon as possible but do not delay transfer to hospital. A normal ECG does not exclude ACS
 - percutaneous coronary intervention (PCI)
 - ⇒ is the first-line and the gold-standard treatment management to revascularise the myocardium.
 - ⇒ but is not available in all centres. Thrombolysis should be performed in patients without access to primary PCI
 - ⇒ offer primary PCI to patients who present within 12 hours of onset of symptoms, if it can be delivered within 120 minutes of the time when fibrinolysis could have been given.
 - ➡ A practical example may be a patient who presents with a STEMI to a small district general hospital (DGH) which does not have facilities for PCI. If they cannot be transferred to a larger hospital for PCI within 120 minutes then fibrinolysis should be given. If the patient's ECG taken 90 minutes after fibrinolysis failed to show resolution of the ST elevation then they would then require transfer for PCI.



Percutaneous coronary intervention (PCI)

- PCI is a technique used to restore myocardial perfusion in patients with ischaemic heart disease, both in patients with stable angina and acute coronary syndromes.
- Stents are implanted in around 95% of patients it is now rare for just balloon angioplasty to be performed
- Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered by endothelium. Until this happens there is an increased risk of platelet aggregation leading to thrombosis.
- Following insertion, the most important factor in preventing stent thrombosis is antiplatelet therapy. Aspirin should be continued indefinitely. The length of clopidogrel treatment depends on the type of stent, reason for insertion and consultant preference
- How long should he continue dual antiplatelet therapy following stent insertion?
 - ⇒ 12 months
 - When dual therapy is maintained for less than 12 months, early cessation of clopidogrel is associated with an increased risk of further ischaemic events.
 - ⇒ Thrombosis of a drug-eluting stent is associated with high morbidity (42%) and mortality (71%). For this reason, dual antiplatelet therapy (usually aspirin and clopidogrel) is continued for at least twelve months following the insertion of this type of stent.
- Elective surgery should be postponed for twelve months when it is considered safe to stop clopidogrel and continue with aspirin.

Complications: Two main complications may occur

- 1. Stent thrombosis:
 - ⇒ due to platelet aggregation as above.
 - ⇒ Occurs in 1-2% of patients, most commonly in the first month.
 - ⇒ Usually presents with acute myocardial infarction
 - ⇒ Treated by **primary angioplasty.**

2. Restenosis:

- ⇒ due to excessive tissue proliferation around stent.
- ⇒ Occurs in around 5-20% of patients, most commonly in the first 3-6 months.
- ⇒ Usually presents with the recurrence of angina symptoms.
- ⇒ Risk factors include diabetes, renal impairment and stents in venous bypass grafts
 - In patients with type-2 diabetes, uncoated coronary stents are liable to re-stenosis at a rate of 40–50% by the end of a 6-month

⇒ Drug eluting stents have been shown to reduce the relative risk of re-stenosis by around 80%, but only where dual anti-platelet therapy with clopidogrel and aspirin is continued for at least 1 year.

Types of stent

- bare-metal stent (BMS)
- drug-eluting stents (DES): stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this reduces restenosis rates the stent thrombosis rates are increased as the process of stent endothelisation is slowed

Thrombolysis

Thrombolysis is no longer indicated except in the context of **STEMI** where **PCI** is not available within 90 minutes of first medical contact.

- **ECG criteria for thrombolysis** within 24 hours of typical pain include:
 - ⇒ ST elevation of more than 1 mm in in two adjacent limb leads.
 - ⇒ ST elevation more than 2 mm in in two adjacent anterior chest leads.
 - ⇒ new left bundle branch block.
- Pre-hospital thrombolysis is indicated if the time from the initial call to arrival at hospital is likely to be over 30 minutes.
 - When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with STEMI should receive immediate (prehospital or admission) thrombolytic therapy
 - ⇒ (NICE) recommends using <u>intravenous bolus</u> (reteplase or tenecteplase) rather than an infusion for pre-hospital thrombolysis
- Thrombolics
 - ⇒ tissue plasminogen activator (tPA) has been shown to offer clear mortality benefits over streptokinase
 - ⇒ streptokinase
 - mechanism of action → Combining with plasmingen to form a complex
 - Streptokinase forms a 1:1 complex with plasminogen that induces structural changes in the protein that activates it without direct cleavage of the Arg-Val bond. it is not specific for fibrin-bound plasminogen.
 - ⇒ alteplase
 - Unlike streptokinase, alteplase activates plasminogen bound to fibrin without activating unbound plasminogen proteins.
 - it is not associated with hypotension or allergic reactions like streptokinase.
 - It has a much shorter half-life of only 3-4 minutes compared to 18 minutes for streptokinase.
 - ⇒ tenecteplase
 - easier to administer
 - has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile
- ECG should be performed 90 minutes following thrombolysis to assess whether there has been a greater than 50% resolution in the ST elevation
 - ⇒ if there has not been adequate resolution then rescue PCI is superior to repeat thrombolysis
 - ⇒ for patients successfully treated with thrombolysis PCI has been shown to be beneficial. The optimal timing of this is still under investigation
- Contraindications to thrombolysis include:
 - ⇒ Gastrointestinal (GI) bleeding in the preceding three weeks.
 - ⇒ Heavy vaginal bleeding
 - ⇒ Ischaemic stroke in last six months
 - ⇒ Previous history of hemorrhagic stroke
 - ⇒ Uncontrolled severe hypertension

- ⇒ Prolonged cardiopulmonary resuscitation (CPR) (more than half an hour).
- ⇒ Known or suspected aortic dissection
- ⇒ Known bleeding disorder
- ⇒ Major surgery or serious trauma within two weeks.
- ⇒ Lumbar puncture in the preceding week.

Relative contraindications

- ⇒ Proliferative diabetic retinopathy,
- ⇒ allergy and
- ⇒ oral anticoagulants

Risk factors for bleeding

- ⇒ Advancing age
- ⇒ Renal impairment
- ⇒ Low body weight and
- ⇒ Known bleeding problems.

Management of hyperglycaemia in acute coronary syndromes

- the most appropriate treatment for his glycaemic control → Commence intravenous insulin infusion and stop metformin
 - ⇒ metformin → increased risk of lactic acidosis.
- Nice in 2011 recommends using a dose-adjusted insulin infusion with regular monitoring of blood glucose levels to glucose below 11.0 mmol/l
- The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study
 demonstrated significant reductions in mortality in subjects with diabetes and
 myocardial infarction (MI) treated with IV insulin infusion (followed by three months of sc
 insulin) compared with conventional therapy with their oral hypoglycaemic agents.
 - intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium, sometimes referred to as 'DIGAMI') regimes are not recommended routinely

MRCPUK-part-1-january-2018: What is the mode of action of alteplase?

- Plasminogen activator
 - Induce conversion of plasminogen to plasmin leading to the dissolution of a fibrin clot.

Myocardial infarction: complications

Complete heart block following a MI? - right coronary artery lesion

Complete heart block following an inferior MI is NOT an indication for pacing, unlike with an anterior MI

Myocardial infarction complications

Complication	Notes	
Cardiac arrhythmia	Occurs within the first few days after MI. Important cause of death before reaching the hospital and within the first 24 hours post-MI. Ventricular fibrillation is the most common cause of death following a MI. Atrioventricular block is more common following inferior myocardial infarctions.	
LV failure and pulmonary oedema	Can occur 2° to LV infarction, VSD, free wall rupture, papillary muscle rupture with mitral regurgitation.	
Post infarction fibrinous pericarditis	1–3 days: common around 10% of patients. friction rub	
Papillary muscle rupture (leads to acute mitral regurgitation).	2–7 days: posteromedial papillary muscle rupture. ↑ risk due to single blood supply from posterior descending artery. More common with infero-posterior infarction. Suddenly develops pulmonary oedema and a loud systolic murmur at the apex which radiated into the axilla with associated pulmonary oedema. often require emergency surgical repair.	
Interventricular septal rupture	3–5 days: macrophage-mediated degradation →VSD →↑ O2 saturation and pressure in RV. acute heart failure associated with a pan-systolic murmur. An echocardiogram is diagnostic and will exclude acute mitral regurgitation which presents in a similar fashion. Urgent surgical correction is needed.	
Ventricular pseudoaneurysm formation	3–14 days: free wall rupture contained by adherent pericardium or scar tissue; low cardiac output, risk of arrhythmia, embolus from mural thrombus.	
True ventricular aneurysm	2 weeks to several months: outward bulge with contraction ("dyskinesia"), associated with fibrosis. typically associated with persistent ST elevation and left ventricular failure. Thrombus may form within the aneurysm increasing the risk of stroke. Patients are therefore anticoagulated.	
Ventricular free wall rupture	5–14 days: present with acute heart failure secondary to cardiac tamponade (raised JVP, pulsus paradoxus, diminished heart sounds). LV hypertrophy and previous MI protect against free wall rupture. Urgent pericardiocentesis and thoracotomy are required.	
Dressler syndrome	Several weeks: autoimmune phenomenon resulting in fibrinous pericarditis. characterised by a combination of fever, pleuritic pain, pericardial effusion, friction rub on auscultation and a raised ESR. Treated with NSAIDs.	
Chronic heart failure	The most important factor predicting outcomes post-STEMI is the presence of new systolic heart failure.	

Primary prevention

drugs which have evidence for the reduction of risk of developing a cardiac event?

- Angiotensin converting enzyme inhibitor
 - ⇒ The most appropriate treatment to reduce cardiovascular risk should focus on adequate blood pressure control
 - ⇒ ↓ BP is most important than control of DM and lipids in CV risk reduction
- Aspirin
- Metformin
 - ⇒ treatment of overweight, diabetic patients with metformin, lowers the relative risk of (MI) by 40%, as opposed to treatment with sulphonylureas or insulin.
- Statins

Myocardial infarction: secondary prevention

Patients with established CVD should take atorvastatin 80mg on

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → renal artery stenosis - do MR angiography

All patients should be offered the following drugs:

- dual antiplatelet therapy (aspirin plus a second antiplatelet agent)
- ACE inhibitor
- beta-blocker
- statin

Some selected lifestyle points:

- Diet:
 - ⇒ advise a Mediterranean style diet, switch butter and cheese for plant oil-based products.
 - ⇒ Do not recommend omega-3 supplements or eating oily fish
- Exercise:
 - ⇒ advise 20-30 mins a day until patients are 'slightly breathless'
- Sexual activity
 - ⇒ may resume 4 weeks after an uncomplicated MI.
 - ⇒ Reassure patients that sex does not increase their likelihood of a further MI.
 - ⇒ PDE5 inhibitors (e.g, sildenafil) may be used 6 months after a MI.
 - They should however be avoided in patient prescribed either nitrates or nicorandil

Clopidogrel

- STFMI:
 - ⇒ the European Society of Cardiology recommend dual antiplatelets for 12 months. In the UK this means aspirin + clopidogrel
- Non-ST segment elevation myocardial infarction (NSTEMI):
 - following the NICE 2013 guidelines, clopidogrel should be given for the first 12 months

Aldosterone antagonists

 patients who have had an acute MI and who have symptoms and/or signs of <u>heart failure</u> and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment (e.g. eplerenone) should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy

Hyperlipidaemia: management

See endocrinology

Heart failure

Definition

• structural or functional impairment of ventricular filling and/or ejection of blood.

Types

- Heart failure with reduced ejection fraction (HFrEF)
 - ⇒ Reduced contractility → systolic ventricular dysfunction → decreased left ventricular ejection fraction (LVEF) → decreased cardiac output
 - ⇒ Causes include:
 - Damage and loss of myocytes (e.g., following myocardial infarction, coronary artery disease, dilated cardiomyopathy)
 - Cardiac arrhythmias
 - High-output cardiac failure
 - A state of heart failure characterized by increased cardiac output and lowered systemic vascular resistance. May be caused by arteriovenous fistulas, renal disease, anemia, beriberi, or Graves' disease.
- Heart failure with preserved ejection fraction (HFpEF)
 - ⇒ Decreased ventricular compliance → diastolic ventricular dysfunction → reduced ventricular filling and increased diastolic pressure → decreased cardiac output (while the left ventricular ejection fraction remains normal)
 - ⇒ Causes include:
 - Increased stiffness of the ventricle (e.g., long-standing arterial hypertension with ventricular wall hypertrophy, restrictive cardiomyopathy)
 - Impaired relaxation of the ventricle (e.g., constrictive pericarditis, pericardial tamponade)

NYHA classification

- The New York Heart Association (NYHA) classification is widely used to classify the severity of heart failure:
 - ⇒ NYHA Class I
 - no symptoms
 - no limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations
 - ⇒ NYHA Class II
 - mild symptoms
 - slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea
 - ⇒ NYHA Class III
 - moderate symptoms
 - marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms
 - ⇒ NYHA Class IV
 - severe symptoms
 - unable to carry out any physical activity without discomfort: <u>symptoms of</u>
 <u>heart failure are present even at rest with</u> increased discomfort with any
 physical activity

Diagnosis (NICE 2010)

- Patient with previous myocardial infarction
 - ⇒ arrange echocardiogram within 2 weeks
 - if <u>transthoracic</u> doppler 2D echocardiography imaging is poor (eg: in obese)
 - → consider other imaging methods, such as:
 - radionuclide angiography,
 - cardiac magnetic resonance imaging or
 - trans-oesophageal Doppler 2D echocardiography.
- No previous myocardial infarction
 - ⇒ measure serum natriuretic peptides (BNP)
 - if levels are 'high' (> 400) arrange echocardiogram within 2 weeks
 - if levels are 'raised' (100-400) arrange echocardiogram within 6 weeks → 40% of patients with raised BNP will have left ventricular systolic dysfunction on echo. the remaining will have other cardiac abnormalities.
 - if levels are 'normal' (< 100) hear failure is unlikely (investigate for other causes)

B-type natriuretic peptide (BNP)

- Source
 - ⇒ produced mainly by the left ventricular myocardium in response to strain.
- Effect
 - ⇒ The net effect of these peptides is:
 - JBP (due to the decrease in systemic vascular resistance) and, thus, afterload on the heart.
 - \understand cardiac output (due to an overall decrease in central venous pressure) and
 preload as a result of the reduction in blood volume that follows natriures is
 and diures is
- Uses
 - ⇒ normal level rules out acute heart failure in the emergency setting
 - ⇒ Very high levels are associated with a poor prognosis.
- Excretion
 - ⇒ Less than 5% of BNP is cleared renally whereas NT-proBNP is reliant solely on the kidney for excretion and hence it is unreliable in patients with coexistent renal dysfunction.

	BNP	NTproBNP
High levels	> 400 pg/ml (116 pmol/litre)	> 2000 pg/ml (236 pmol/litre)
Raised levels	100-400 pg/ml (29-116 pmol/litre)	400-2000 pg/ml (47-236 pmol/litre)
Normal levels	< 100 pg/ml (29 pmol/litre)	< 400 pg/ml (47 pmol/litre)

Diagnosis of acute heart failure (Nice guidelines 2014):

- In people presenting with new suspected acute heart failure:
 - ⇒ rule out the diagnosis of heart failure if :
 - BNP less than 100 ng/litre
 - NT- proBNP less than 300 ng/litre.
 - ⇒ new suspected acute heart failure **with** raised natriuretic peptide levels → perform transthoracic Doppler 2D echocardiography (within 48 hours of admission)

Factors, which alter the BNP level:

Increase BNP levels	Decrease BNP levels
 Left ventricular hypertrophy Aortic stenosis, Hypertension Ischaemia Tachycardia Right ventricular overload Hypoxaemia (including pulmonary embolism) GFR < 60 ml/min Sepsis COPD, Cor pulmonale Diabetes Age > 70 Liver cirrhosis Hyperaldosteronism Cushing's syndrome Stable angina, Acute coronary syndromes Atrial fibrillation (AF) 	 Obesity Diuretics ACE inhibitors Beta-blockers Angiotensin 2 receptor blockers Aldosterone antagonists

Mechanism of central sleep apnea (CSA) in HF:

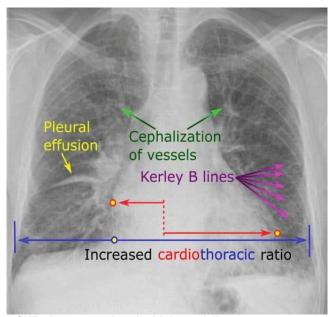
- Which mechanism is responsible for the patient's polysomnography findings in heart failure?
 - ⇒ **Increased sensitivity to carbon dioxide** and stimulation of the vagal receptors.
 - ⇒ increased sensitivity to PaCO₂ is a protective mechanism from hypercapnia due to heart failure.
 - HF → ↑duration of circulation of blood gases from the lungs to the brain.
 - When these blood gases reach the brain, the increased sensitivity to PaCO₂ → higher-than-normal response of hyperventilation → ↓PaCO₂ lower than the apneic threshold.
 - As soon as the brain detects low PaCO₂ it will cease ventilation with apnea (central) so PaCO₂ can rise again.
 - As soon as the PaCO₂ rises again and reaches the brain (longer than normal due to heart failure), it will cause another episode of hyperventilation.
 - ⇒ supine position → ↑ venous return → pulmonary congestion → activate vagal receptors → hyperventilation.

Hyponatraemia in patients with CHF

- Water restriction is the first-line and mainstay of therapy
- Stopping furosemide will not be possible for a patient who has decompensated heart failure.
- Similarly, administration of hypertonic saline is only indicated if there is neurological manifestation of hyponatremia.
- Moreover hypertonic or isotonic saline administration will be poorly tolerated in a volumeoverloaded patient.
- associated with the worst prognosis

Investigations

- Chest x-ray: Features of pulmonary oedema on a chest x-ray may include:
 - ⇒ interstitial oedema
 - ⇒ bat's wing appearance
 - ⇒ upper lobe diversion (increased blood flow to the superior parts of the lung)
 - ⇒ Kerley B lines
 - ⇒ pleural effusion
 - ⇒ cardiomegaly may be seen if there is cardiogenic cause



Typical CXR signs associated with heart failure

The most common cause of flash pulmonary oedema is myocardial ischaemia.

Bilateral renal artery stenosis is a less common cause of flash pulmonary oedema.

Pharmacological management

Acute heart failure management

- Initial pharmacological treatment
 - ⇒ intravenous diuretics
- Initial non-pharmacological treatment
 - ⇒ cardiogenic pulmonary oedema with severe dyspnoea and acidaemia consider starting non-invasive ventilation
 - in this case it is the most useful next step, before diuretics. The effect of the diuresis comes much later and has a modest overall contribution in managing the symptoms of shortness of breath.
 - Consider invasive ventilation in acute heart failure that, despite treatment, is leading to or is complicated by: respiratory failure or reduced consciousness or physical exhaustion.

In a person presenting with acute heart failure who is already taking beta-blockers:

- continue the beta-blocker treatment unless they have a heart rate less than 50 beats per minute, second or third degree atrioventricular block, or shock.
- restart beta-blockers once their condition has been stabilised for example, when intravenous diuretics are no longer needed.

In a person presenting with acute heart failure who is already taking frusemide 80 mg:

 in a patient with evidence of decompensated heart failure and fluid overload. The most appropriate initial management is to Increase furosemide and relieve the symptoms of fluid overload – pulmonary and peripheral oedema.

Chronic management

- 4 drugs have been shown to improve mortality in patients with chronic heart failure:
 - 1. ACE inhibitors
 - 2. spironolactone
 - 3. beta-blockers
 - 4. hydralazine with nitrates
- No long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide.
- In patients with symptoms of heart failure not controlled on ACE inhibitors alone, switching
 to the combination of ARB and neprilysin inhibitor can further improve symptoms and
 quality of life.
 - ⇒ e.g: combination of sacubitril and valsartan reduced cardiovascular death and heart failure hospitalisations by 20%.
- NICE issued updated guidelines on management in 2010, key points include:
 - ⇒ first-line treatment for all patients is both an ACE-inhibitor and a beta-blocker
 - With the persisting symptoms despite 80 mg of furosemide, guidelines would initially suggest the addition of an ACE inhibitor.
 - Although beta-blockers would be of further benefit in this patient, it is important first to establish him on ACEi and then introduce betablockers like carvedilol, metoprolol or bisoprolol in a small dose and gradually increase.
 - ⇒ second-line treatment is now either an aldosterone antagonist, angiotensin II receptor blocker or a hydralazine in combination with a nitrate
 - if symptoms persist cardiac resynchronisation therapy or digoxin should be considered
 - digoxin has also not been proven to reduce mortality in patients with heart failure
 - It may however improve symptoms due to its inotropic properties.
 - Digoxin is strongly indicated if there is coexistent atrial fibrillation
 - There is no evidence that increasing a dose of digoxin above 62.5 µg in a patient in sinus rhythm would have any added benefit.
 - ⇒ diuretics should be given for fluid overload
 - ⇒ offer annual influenza vaccine
 - ⇒ offer one-off pneumococcal vaccine
 - adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years

Drugs that improve prognosis are beta blockers, ACE inhibitors, ARNIs, aldosterone antagonists, and hydralazine with nitrate.

MRCPUK-part-1-jan-2018: In a patient with significant heart failure on maximum medical therapy (ramipril 10 mg OD, furosemide 80 mg OD, bisoprolol 10 mg OD and spironolactone 25 mg OD). Despite this, they have continued to deteriorate but criteria for cardiac resynchronisation therapy (CRT) are not achieved. What is the most appropriate next step to improve mortality?

Ivabradine

- acts as an inhibitor of the I_f current within the myocardium. This current, particularly
 present in the sino-atrial and atrio-ventricular nodes, acts as the cardiac pacemaker.
- By inhibiting this current, ivabradine reduces the heart rate without impacting the force of cardiac contraction.
- This has been shown to reduce heart failure hospitalisation and mortality in patients already on maximum medical therapy.
- Due to its mechanism, ivabradine is only effective in patients in sinus rhythm.

What is the management of a patient with severe CHF who develops gynecomastia? Switch spironolactone to eplerenone.

If known case of heart failure – on β -blocker – presented with acute pulmonary oedema \rightarrow Increase diuretics, stop β -blockers and restart β -blockers when his lungs are dry.

A significant benefit from using IV iron in patients with heart failure and iron deficiency was demonstrated in a study

history of heart failure + iron deficiency. the first step → correcting iron deficiency

Non- pharmacological management

- Cardiac resynchronisation therapy (CRT) (biventricular pacing): criteria for resynchronisation therapy recommended by NICE guidance
 - 1. They are in sinus rhythm +
 - either with a QRS duration of ≥ 150 ms estimated by ECG (LBBB)
 - or with a QRS duration of 120-149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography
 - 2. They have a left ventricular ejection fraction of ≤ 35%.
 - **3.** They are receiving optimal pharmacological therapy.
- Benefit: Improved symptoms and reduced hospitalisation in NYHA class III patients
- Investigations: the most useful investigation in predicting symptomatic response to cardiac resynchronisation therapy is → transthoracic echocardiogram and ECG (The echo will show asynchronous contraction of the LV and RV and subsequently reduced ejection fraction).
- Complications: When a CRT device is implanted the left ventricular lead is inserted in the
 coronary sinus. To obtain access to the coronary sinus a catheter with an aggressive tip is
 used. There is a 1% risk of causing dissection/perforation to the coronary sinus
 which can lead to cardiac tamponade.

Implantable cardioverter defibrillator (ICD)

 Where there is no LBBB and QRS is between 120-149 ms, ICD is the recommended option according to NICE guidelines. This is because of the risk of VT on account of the low ejection fraction, (<35%), and symptomatic heart failure.

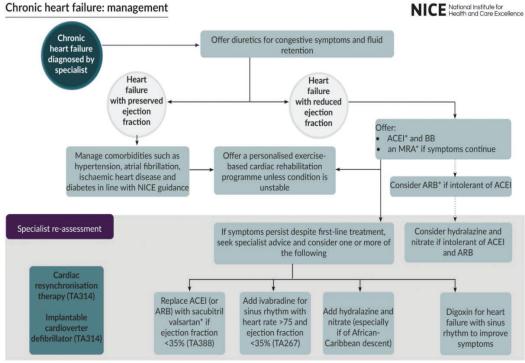
Exercise training

improves symptoms but not hospitalisation/mortality

Tocolysis-associated pulmonary oedema

- Tocolytics are medications administered for the suppression of premature contractions.
- Acute pulmonary oedema can occur with administration of β_2 agonists for tocolysis in up to 5–15% of cases.
- It usually occurs after 24 h of administration of these agents.
- The chest X-ray reveals pulmonary infiltrates and normal heart size.
- Concomitant use of corticosteroids that are often administered for lung maturation have also been implicated as risk factor for development of tocolysis-associated pulmonary oedema.
- Treatment involves stopping the tocolytics, oxygen and careful volume control.
- Deferential:
 - ⇒ Peripartum cardiomyopathy:
 - typically presents in the last month of pregnancy and up-to 6 months postpartum.
 - cardiomegaly on chest X-ray.

NICE management summery



Other management options

If heart failure is caused or worsened by **other conditions**, these should be managed appropriately:

- Revascularisation (e.g. coronary artery bypass grafting)
- Valve surgery (e.g. aortic valve replacement)
- Implantable cardiac defibrillator (ICD): inserted if EF <30% for prevention of fatal arrhythmias
- Cardiac resynchronisation therapy + defibrillator (CRT-D): a biventricular pacemaker for EF <30% + QRS >130 m/sec to re-synchronise left and right ventricular contraction to improve EF
- Cardiac transplantation is rare and strict criteria must be met for consideration.
 - ⇒ By five years following cardiac transplantation, nearly all patients have some degree of small coronary vascular narrowing (Coronary arteriopathy).

Potentially harmful drugs to avoid in heart failure

Drug to avoid	Notes
Non-steroidal anti-inflammatory drugs (NSAIDs)	May cause sodium and water retention, peripheral vasoconstriction, worsen heart failure, and decrease renal function.
	Acute renal failure may be more likely when these agents are used in combination with an ACE inhibitor (ACEI) / angiotensin receptor blocker (ARB) and/or diuretic.
Non-dihydropyridine calcium channel blockers –verapamil and diltiazem1	 Negative inotropic effect may further depress cardiac function. Risk is greatest with verapamil, then diltiazem and least risk with dihydropyridines, but use with caution
	Non-dihydropyridine calcium channel blockers are contraindicated in systolic heart failure, but may be useful in heart failure with preserved ejection fraction where slowing heart rate can increase filling time
Tricyclic antidepressants	May prolong QT interval and cause arrhythmias as well as hypotension from alpha-blocking effects
Thiazolidinediones (e.g. pioglitazone)	May cause fluid retention and heart failure by increasing renal sodium reabsorption
Corticosteroids	May worsen heart failure due to sodium and water retention (mineralocorticoid effect)
Clozapine	May cause cardiomyopathy and myocarditis
Oncology treatments such as anthracyclines (doxorubicin, daunorubicin), trastuzumab	may cause heart failure
Tumour necrosis factor antagonists (e.g. infliximab, etanercept)	May cause heart failure
Moxonidine (centrally acting antihypertensive)	Contraindicated in heart failure. Associated with increased mortality in heart failure

Prognosis

- Prognosis is poor overall, with approximately 50% of people with heart failure dying within five years of diagnosis
- Factors indicating worse prognosis in heart failure
 - ⇒ High BNP/NT-pro-BNP
 - ⇒ Anaemia
 - ⇒ Hyponatraemia
 - ⇒ Increased uric acid.

Mechanical support with the insertion of an intra-aortic balloon pump (IABP) in patient with Cardiogenic shock

- In case with hypotension and cardiogenic shock, what is the most appropriate intervention after failure of an inotropic support treatment?
 - ⇒ Intra-aortic balloon counter pulsation (IABCP) to support cardiac output.
- An intra-aortic balloon pump is inserted under echocardiographic quidance. At which point of the ECG should balloon inflation be timed?
 - ⇒ Middle of the T wave
 - Balloon inflation is timed with diastole once closure of the aortic valve has occurred: this corresponds to the middle of the T wave.
- What is the contraindication to placement of an intra-aortic balloon pump?
 - ⇒ For blood to be ejected antegrade to perfuse the tissues and retrograde to perfuse the coronaries, the aortic valve must be closed and competent. Aortic regurgitation is therefore a contraindication to placement of an intra-aortic balloon pump.

Hypertrophic obstructive cardiomyopathy (HOCM)

HOCM is the most common cause of sudden cardiac death in the young

- . (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins.
- The most common defects involve a mutation in the gene encoding β-myosin heavy chain protein or myosin binding protein C.
- Mutations to various proteins including beta-myosin, alpha-tropomyosin and troponin T have been identified.
- type of mutation → Frame-shift mutation
- The estimated prevalence is 1 in 500.
- Septal hypertrophy causes left ventricular outflow obstruction.
- It is an important cause of sudden death in apparently healthy individuals.

Protein	Percentage
Beta-myosin heavy chain	35
Myosin-binding protein C	15
Troponin T	15
Alpha-tropomyosin	1
Myosin light chain	1

Mutations known to cause hypertrophic cardiomyopathy.

Features

Sudden death, unusual collapse in young person - ? HOCM

Symptoms and signs are similar to those of aortic stenosis, except that the character of the pulse in HOCM is jerky

- often asymptomatic
- dyspnea (the most common presenting symptom)
- angina,
- syncope
- · sudden death (most commonly due to ventricular arrhythmias), arrhythmias, heart failure
- jerky pulse,
- · large 'a' waves,
- · double apex beat
- ejection systolic murmur: increases with Valsalva manoeuvre and decreases on squatting
 - ⇒ Diastolic decrescendo murmur of aortic regurgitation (10% of patients)

Associations

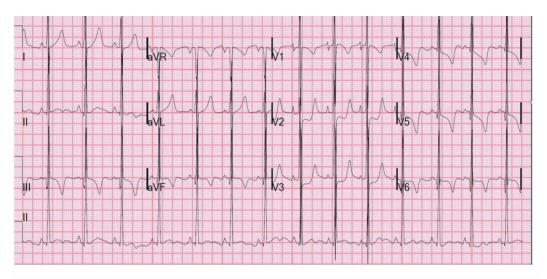
- · Friedreich's ataxia
- Wolff-Parkinson White

Echo - mnemonic - MR SAM ASH

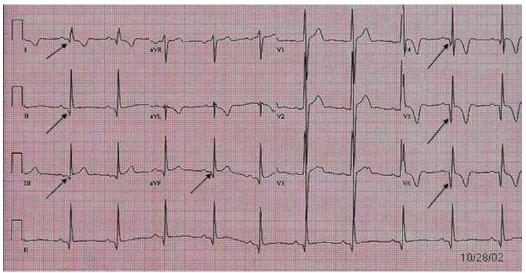
- mitral regurgitation (MR)
- systolic anterior motion (SAM) of the anterior mitral valve leaflet
- asymmetric hypertrophy (ASH)

ECG

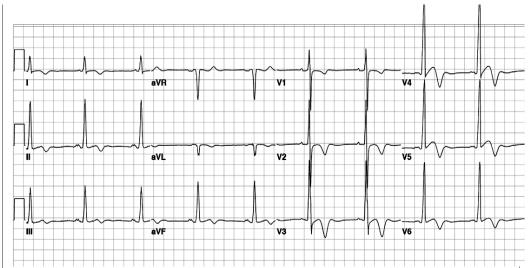
- left ventricular hypertrophy
- progressive T wave inversion
- deep Q waves
- right or left axis deviation
- PR prolongation
- · atrial fibrillation may occasionally be seen
- Right bundle branch block
 - ⇒ the most ECG FINDING which support a diagnosis of HOCM
 - ⇒ RBBB is correlated with anterior, anteroseptal and mid-septal myocardial fibrosis in HOCM.



ECG showing typical changes of HOCM including LVH and T wave inversion



Dagger-like Q waves



This ECG shows the typical pattern of apical HCM:

- Large precordial voltages.
- Giant T wave inversions in the precordial leads
- Inverted T waves are also seen in the inferior and lateral leads.

Type of cardiomyopathy	Selected points
Hypertrophic obstructive cardiomyopathy	 Leading cause of sudden cardiac death in young athletes Usually due to a mutation in the gene encoding β-myosin heavy chain protein Common cause of sudden death Echo findings include:
Arrhythmogenic right ventricular dysplasia	Right ventricular myocardium is replaced by fatty and fibrofatty tissue Around 50% of patients have a mutation of one of the several genes which encode components of desmosome ECG abnormalities in V1-3, ⇒ typically T wave inversion. ⇒ An epsilon wave is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex

Management

- Amiodarone
- Beta-blockers or verapamil for symptoms
- Cardioverter defibrillator
- **D**ual chamber pacemaker
- Endocarditis prophylaxis

Beta-blockers

- · Generally first-line agents
 - ⇒ increase diastolic filling and decrease contractility
 - ⇒ Reduces provocable gradient

disopyramide

- If B-blockers alone are ineffective, disopyramide, may be added (Class IA antiarrhythmic drug)
- anticholinergic side-effects include dryeyes and mouth, urinary hesitancy or retention, and constipation.
- QTc interval should be monitored during dose up-titration and the dose reduced if it exceeds 480 ms.
- Disopyramide should be avoided in patients with glaucoma, prostatism, and in patients taking other drugs that prolong the QT interval, such as amiodarone and sotalol.

Verapamil

- Verapamil (starting dose 40 mg three times daily to maximum 480 mg daily) can be used when ß-blockers are contraindicated or ineffective,
- close monitoring is required in patients with severe obstruction (≥100 mm Hg) or elevated pulmonary artery systolic pressures, as it can provoke pulmonary oedema.
- Verapamil should however be avoided in HOCM patients with coexistent Wolff Parkinson White as it may precipitate VT or VF.

Implantable cardioverter defibrillators (ICD) implantation → prevention of sudden cardiac death

 recommended in patients who have survived a cardiac arrest due to VT or VF or who have spontaneous sustained VT causing syncope or haemodynamic compromise

Invasive treatment (myomectomy or alcohol septal ablation) (ESC Guidelines 2014)

- Left ventricular outflow tract obstruction (LVOTO) is defined as a peak instantaneous
 Doppler LV outflow tract gradient of ≥30 mm Hg, but the threshold for invasive treatment is
 usually considered to be ≥50 mm Hg.
- Septal reduction therapy is recommended in patients with LVOT gradient of ≥ 50 mm Hg, who are in NYHA functional Class III–IV, despite maximum tolerated medical therapy.
- The most commonly performed surgical procedure used to treat LVOTO is ventricular septal myectomy (Morrow procedure).
- Pre-operative determinants of a good long-term outcome are age < 50 years, left atrial size
 46 mm, absence of atrial fibrillation and male gender.
- surgery VS septal alcohol ablation (SAA)
 - ⇒ both procedures improve functional status with a similar procedural mortality.
 - ⇒ Septal alcohol ablation is associated with a higher risk of AV block, requiring permanent pacemaker implantation and larger residual LV outflow tract gradients.
 - ⇒ In contrast to myectomy, most patients develop right-, rather than left bundle branch block after SAA.

Drugs to avoid

- nitrates
- ACE-inhibitors
- Inotropes : Digoxin

Poor prognostic factors, which are predictive of sudden cardiac death

HOCM - poor prognostic factor on echo = septal wall thickness of > 3cm

- syncope
- · family history of sudden death
- Maximum left ventricular wall thickness greater than 3 cm
- young age at presentation
- non-sustained ventricular tachycardia on 24 or 48-hour Holter monitoring
- Abnormal blood pressure changes on exercise (Blood pressure drop during peak exercise on stress testing).

Screening of HOCM

- Current guidelines suggest that a resting ECG and TTE (transthoracic ECHO) are the most effective screening strategies for relatives of patients with HOCM.
- Genetic testing is not recommended as a first line screening tool given varying rates of penetrance.

Dilated cardiomyopathy (DCM)

Overview

- Most common cardiomyopathy
- Sex: ♂ > ♀ (approx. 3:1)
- dilated heart leading to systolic (+/- diastolic) dysfunction
- all 4 chambers affected but LV more so than RV

Features

- arrhythmias,
- emboli → cardio-embolic stroke,
- mitral regurgitation
- · absence of congenital, valvular or ischaemic heart disease

Causes

- Common causes
 - ⇒ Idiopathic (approx. 50%)
 - ⇒ alcohol: may improve with thiamine
 - ⇒ postpartum
 - ⇒ hypertension
- Other causes
 - ⇒ genetic inherited dilated cardiomyopathy:
 - around third of DCM patients
 - <u>the majority</u> of defects are inherited in an <u>autosomal dominant</u> fashion although other patterns of inheritance are seen
 - ⇒ infections e.g. Coxsackie B, HIV, diphtheria, parasitic
 - ⇒ endocrine e.g. Hyperthyroidism
 - ⇒ neuromuscular e.g. Duchenne muscular dystrophy
 - ⇒ nutritional e.g. Kwashiorkor, pellagra, thiamine/selenium deficiency
 - Selenium deficiency is one of the reversible causes of dilated cardiomyopathy.
 - ⇒ druas e.a. Doxorubicin
 - ⇒ Infiltrative (may also lead to restrictive cardiomyopathy) e.g. Haemochromatosis, Sarcoidosis

Diagnosis → Echocardiogram

- The echo may show:
 - ⇒ Reduced left ventricular ejection fraction,
 - ⇒ myocardial dyssynchrony (myocardial segments contract at different points in time),
 - ⇒ thinning of the left ventricular wall
 - ⇒ dilated left ventricle.

Type of cardiomyopathy	Selected causes/points
Dilated cardiomyopathy	Classic causes include
Restrictive cardiomyopathy	Classic causes include

Becker's muscular dystrophy

- X-linked recessive disorder resulting from a mutation in the dystrophin gene.
- The clinical picture is similar to that of Duchenne's muscular dystrophy but it is much milder.
- Patients usually present between the ages of 5 and 15 years, though presentation may not be until the fourth or fifth decade.
- Patients may present with heart failure secondary to <u>dilated cardiomyopathy</u> rather than the classic proximal muscle weakness.

Restrictive cardiomyopathy

Restrictive cardiomyopathy: amyloid (most common), haemochromatosis, Loffler's syndrome, sarcoidosis, scleroderma

Causes

- amyloidosis (e.g. secondary to myeloma) most common cause in UK
 - Cardiac involvement is the most common cause of death in patients with amyloidosis associated with an immunocyte dyscrasia - typically as restrictive cardiomyopathy
 - ⇒ <u>Transthyretin gene</u> mutations can lead to restrictive cardiomyopathy from amyloid deposition in the heart.
 - Diagnosis is confirmed by myocardial biopsy, which shows amyloid infiltration when stained with Congo Red.
 - myocardial biopsy, which when stained with Congo Red will show "apple green birefringence" amyloid under polarized light.
- haemochromatosis
- Loffler's syndrome
- sarcoidosis
- scleroderma
- Radiotherapy
- Systemic sclerosis
- Carcinoid syndrome.

Pathophysiology:

 Proliferation of connective tissue → ↓ elasticity of myocardium → ↓ ventricular compliance → ↓ diastolic filling → atrial congestion → atrial enlargement and severe diastolic dysfunction

Features

- Physical examination reveals right heart failure with a raised JVP, characteristically showing a prominent deep Y descent
- · Heart size is often normal.
- S 4 heart sound, due to ventricular noncompliance.
- Pericardial effusion is common, but rarely causes tamponade
- The most characteristic ECG finding of restrictive cardiomyopathy is diffusely diminished voltages
- Echocardiography findings
 - ⇒ small thick ventricles and a thick interatrial septum due to amyloid deposits, which have a 'granular sparkling' appearance
 - Amyloid deposits in the heart produce generalized thickening of the myocardium (as opposed to asymmetrical septal hypertrophy commonly seen in hypertrophic cardiomyopathy) and diastolic dysfunction.
 - ⇒ impaired relaxation in the diastolic phase.
 - ⇒ bright speckled appearance.

Differential diagnosis

- · constrictive pericarditis
 - ⇒ Features are very similar in constrictive pericarditis, but in constrictive pericarditis:
 - the apex is frequently non-palpable due to the thick pericardium
 - chest X-ray may show pericardial calcifications

Features suggesting restrictive cardiomyopathy rather than constrictive pericarditis

- prominent apical pulse
- · absence of pericardial calcification on CXR
- heart may be enlarged
- ECG abnormalities e.g. bundle branch block, Q waves

Clinical Features of Constrictive Pericarditis and Restrictive Cardiomyopathy

Clinical Features	Constrictive Pericarditis	Restrictive Cardiomyopathy
History	Prior history of pericarditis or condition that causes pericardial disease	History of systemic disease (eg, amyloidosis, hemochromatosis)
Systemic examination - Heart sounds	Pericardial knock, high-frequency sound	Presence of loud diastolic filling sound S ₃ , Low-frequency sound
Murmurs	No murmurs	Murmurs of mitral and tricuspid insufficiency
apical pulse	apex is frequently non-palpable due to the thick pericardium	prominent apical pulse
Prior chest radiograph	Pericardial calcification	Normal results of prior chest radiograph

Management

Cardiac transplant

Peripartum cardiomyopathy (PCM)

- biventricular heart failure during the third trimester.
- the aetiology: unknown, although both myocarditis and low levels of dietary selenium have been postulated as causes.

Management

- similar to the management of heart failure in any other situation with vasodilators, diuretics and beta blockade. ACE inhibition is reserved for the post-partum period.
 - ⇒ sodium restriction,
 - ⇒ diuretics to optimise the volume status.
 - ⇒ digoxin and afterload-reducing agents.
 - ⇒ Hydralazine
- For patients presenting with PCM, defined as left ventricular systolic dysfunction 1 month
 prior to delivery or 5 months postpartum, volume status should first be managed with
 diuretics after liaison with obstetricians. Beta-blockers should be added once the
 patient's volume status is optimised.
- Anticoagulation
 - ⇒ Patients with PCM are at risk of thromboembolism due to both hypercoagulable state of pregnancy and stasis of blood in the left ventricle. Therefore, anticoagulation with **heparin** is recommended.

Type of cardiomyopathy	Selected points
Peripartum cardiomyopathy	 Typical develops between last month of pregnancy and 5 months post- partum More common in older women, greater parity and multiple gestations
Takotsubo cardiomyopathy	 'Stress'-induced cardiomyopathy e.g. patient just found out family member dies then develops chest pain and features of heart failure Transient, apical ballooning of the myocardium Treatment is supportive

Takotsubo cardiomyopathy

Definition:

- Takotsubo cardiomyopathy is a type of non-ischaemic cardiomyopathy associated with a transient, apical ballooning of the myocardium.
- · acute, stress-induced, reversible dysfunction of the left ventricle

Epidemiology:

• especially postmenopausal women > 60 years

Pathophysiology:

emotional/physical stress → massive catecholamine discharge → cardiotoxicity, multivessel spasms and dysfunction → myocardial stunning

Features

- · chest pain
- features of heart failure
- ST elevation
- normal coronary angiogram

Treatment

supportive

Prognosis:

spontaneous recovery if stressors are avoided

Congenital heart disease: types

Paradoxical embolus - PFO most common cause - do TOE

Congenital heart disease

cyanotic: TGA most common at birth, Fallot's most common overall

acyanotic: VSD most common cause

Acyanotic - most common causes

- ventricular septal defects (VSD) most common, accounts for 30%
- atrial septal defect (ASD) 10%.
- patent ductus arteriosus (PDA)
- coarctation of the aorta
- · aortic valve stenosis

VSDs are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later

Cyanotic - most common causes

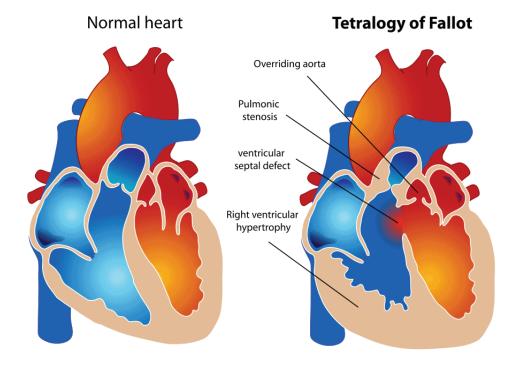
- tetralogy of Fallot
 - ⇒ There is a single sound in Fallot's because of an absent P2.
 - ⇒ A Blalock shunt (anastomosis of subclavian artery to pulmonary artery) used to be performed for Fallot's tetralogy and leads to a weak left radial pulse.
- transposition of the great arteries (TGA)
 - ⇒ **Fallot's** is more common than TGA. However, at birth TGA is the more common lesion as patients with Fallot's generally presenting at around 1-2 months
 - ⇒ TGA is usually treated by prostaglandins in order to keep the ductus arteriosus patent (from pulmonary artery to the descending aorta), so some oxygenated blood can reach systemic circulation.
- · tricuspid atresia
- pulmonary valve stenosis
- Total anomalous pulmonary venous connection (TAPVC)
 - ⇒ TAPVC consists of an abnormality of blood flow in which all four pulmonary veins drain into systemic veins or the right atrium with or without pulmonary venous obstruction.
 - ⇒ Systemic and pulmonary venous blood mix in the right atrium.

Other notes

- Aortic regurgitation may be a feature of osteogenesis imperfecta.
- Ebstein's anomaly is associated with maternal LiCO₃ use if exposed in the first trimester.
- The majority of cases of neonates with complete heart block may be caused by autoimmune disease, particularly anti-ro antibodies in the mother.
- Left ventricle (LV) hypolasia occurs when the left sided chambers fail to develop and blood
 enters the systemic circulation from the right ventricle via the pulmonary artery and a patent
 ductus arteriosus.

Tetralogy of Fallot (TOF)

- TOF is the most common cause of cyanotic congenital heart disease*.
 - ⇒ *however, at birth transposition of the great arteries is the more common lesion as patients with TOF generally present at around 1-2 months
- It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old
- TOF is a result of anterior malalignment of the aorticopulmonary septum. The four characteristic features are:
 - 1. ventricular septal defect (VSD)
 - 2. right ventricular hypertrophy
 - 3. right ventricular outflow tract obstruction, pulmonary stenosis
 - There is a single sound in Fallot's because of an absent P2.
 - 4. overriding aorta



 The severity of the right ventricular outflow tract obstruction determines the degree of cyanosis and clinical severity

Other features

- · cyanosis
- causes a right-to-left shunt
- ejection systolic murmur due to pulmonary stenosis (the VSD doesn't usually cause a murmur)
- a right-sided aortic arch is seen in 25% of patients
- chest x-ray shows a 'boot-shaped' heart, ECG shows right ventricular hypertrophy

Management

- · surgical repair is often undertaken in two parts
- cyanotic episodes may be helped by beta-blockers to reduce infundibular spasm

The most common residual lesion in repaired tetralogy of Fallot is pulmonary regurgitation.

Ventricular septal defects (VSD)

Overview

- The second most common congenital heart defect
 - ⇒ bicuspid aortic valve is the most common congenital heart defect
- They close spontaneously in around 50% of cases.
- the most common site for a VSD → Perimembranous
 - ⇒ Perimembranous VSDs account for 70-80% of VSDs and are situated between the inlet and outlet portions of the septum.

Associations

- Congenital VSDs: associated with:
 - ⇒ chromosomal disorders (e.g. Down's syndrome, Edward's syndrome, Patau syndrome)
- Non-congenital causes include:
 - ⇒ Fetal alcohol syndrome
 - ⇒ Intrauterine infection (e.g., TORCH)
 - ⇒ post myocardial infarction

Features

- Pan-systolic murmur which is:
 - ⇒ louder in smaller defects
 - ⇒ usually loudest at the left lower sternal edge (LSE)
- Mid-diastolic murmur over cardiac apex
 - ⇒ Due to increased flow through the mitral valve
- systolic thrill
- Loud pulmonic S2 (if pulmonary hypertension develops)

Investigations

- Chest x-ray
 - ⇒ Enhanced pulmonary vascular markings
 - ⇒ Left atrial and ventricular enlargement
- ECG
 - ⇒ The clue to diagnosis in the ECG finding → <u>Biventricular hypertrophy</u>
 - Biventricular hypertrophy is classically described as having biphasic QRS complexes in V2-5 which is known as the <u>Katz Wachtel phenomenon</u> and is classic for VSD.
- Doppler echocardiography: confirms diagnosis

Complications

- Aortic regurgitation
 - ⇒ due to a poorly supported right coronary cusp resulting in cusp prolapse
- · Infective endocarditis
- Eisenmenger's complex
- Right heart failure
- Pulmonary hypertension
 - ⇒ pregnancy is contraindicated in women with pulmonary hypertension as it carries a 30-50% risk of mortality.

Treatment

small to moderate defects often heal spontaneously

- Symptomatic and large VSDs → Surgical (patch) repair
- Heart-lung transplant or lung transplant with concurrent VSD repair if Eisenmenger's reaction has occurred

Atrial septal defect (ASD)

- common congenital heart lesion
 - ⇒ VSD is more common

Types

- Ostium secundum
 - ⇒ 70% of ASDs
 - ⇒ associated with Holt-Oram syndrome (tri-phalangeal thumbs)
 - ⇒ ECG: RBBB with RAD
- Ostium primum
 - ⇒ present earlier than ostium secundum defects
 - ⇒ associated with abnormal AV valves
 - ⇒ the AV node is displaced posteriorly and inferiorly and atrial and/or AV nodal conduction is often delayed.
 - ⇒ ECG: RBBB with LAD, prolonged PR interval

wide, fixed, split-second sound + right-axis deviation → Ostium secundum wide, fixed, split-second sound + left-axis deviation → Ostium primum

Features

- Symptoms
 - ⇒ asymptomatic in youth
 - ⇒ often discovered on routine school health exams
 - ⇒ mild fatique
 - ⇒ frequent respiratory infections
 - ⇒ Larger ones may lead to signs of right ventricular failure, such as shortness of breath and a parasternal heave.
- Physical exam
 - ⇒ Mid-systolic ejection murmur (over the left second ICS)
 - Due to → Relative pulmonary stenosis due to an increase in stroke volume
 - ⇒ Soft mid-<u>diastolic</u> murmur (over the lower left sternal border)
 - arises from increased flow across the tricuspid valve.
 - ⇒ loud S1
 - ⇒ wide fixed-split S2
 - The most frequently tested knowledge
 - splitting is fixed (does not vary with respiration)
 - ⇒ heaving cardiac impulse (LLSB)
- Other features
 - ⇒ The grossly elevated D_Lco is secondary to the left-right shunt and increased pulmonary blood flow. In contrast, chronic pulmonary emboli will cause a low D_Lco.

Predisposes patient to

- ➤ CHF
 - 2nd/3rd decades of life
- > Eisenmenger's syndrome
 - pulmonary hypertension
 - right ventricular hypertrophy
 - reversal to a right-to-left shunt
- stroke
 - due to paroxysmal embolus

Associated condition

- Tricuspid atresia is the congenital cardiac disorder most commonly associated with an atrial septal defect.
- Down syndrome
- · Fetal alchohol syndrome
- Holt-Oram syndrome
 - ⇒ Autosomal dominant disorder, which is also called hand-heart syndrome because affected children present with an ASD, a first degree heart block, and abnormalities of the upper limbs (e.g., absent radial bones). It affects approx. 1 in 100,000 children.

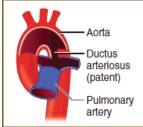
ECG

- Right bundle branch block
- ostium primum ASD →left axis deviation.
- ostium secundum ASD → right axis deviation.
- first degree heart block → prolongation of the PR interval
 - > due to delayed conduction through the atria or through the AV node
- The QRS pattern typically is either an rSr' or an rsR' resulting from dilation and hypertrophy
 of the right ventricular outflow tract caused by volume overload of the right heart.

prominent left precordium in a young patient with an ejection murmur in the second left intercostal space indicat \rightarrow **ASD with pulmonary hypertension**

- ⇒ A prominent left precordium suggests that:
 - the right ventricle was dilated during childhood
 - RV working against a high pressure

Patent ductus arteriosus



"Endomethacin" (indomethacin) ends patency of PDA; PGE kEEps it open (may be necessary to sustain life in conditions such as transposition of the great vessels).

PDA is normal in utero and normally closes only after birth.

Overview

- · acyanotic congenital heart defect
- · connection between the pulmonary trunk and descending aorta
- more common in premature babies, born at high altitude or maternal rubella infection in the first trimester

Features

- · left subclavicular thrill
- continuous 'machinery' murmur at the left upper sternal edge with late systolic accentuation
- large volume, bounding, collapsing pulse
- · wide pulse pressure
- heaving apex beat

Management

- indomethacin closes the connection in the majority of cases
- if associated with another congenital heart defect amenable to surgery then prostaglandin
 E1 is useful to keep the duct open until after surgical repair

Patent foramen ovale (PFO)

- PFO is present in around 20% of the population.
- It may allow embolus (e.g. from DVT) to pass from right side of the heart to the left side leading to a stroke - 'a paradoxical embolus'
- There also appears to be an association between migraine and PFO.
 - ⇒ Some studies have reported improvement in migraine symptoms following closure of the PFO
- right heart catheter: left to right shunting of oxygenated blood at level of the atrium.
 - ⇒ oxygen saturation data show a step-up in the saturations between the vena cava and the right atrium.

Paradoxical embolisation

- For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart.
- · The following cardiac lesions may cause such events
 - > patent foramen ovale present in around 20% of the population
 - > atrial septal defect a much less common cause

Blue toe syndrome

- 80% of digital ischaemias have an emboli originating from the heart and so an urgent echocardiogram is crucial to prevent further and more severe events occurring.
- sudden onset of a cold, painful, and cyanotic big toe. the next steps → Therapeutic heparin and urgent echocardiogram

Eisenmenger's syndrome

Eisenmenger's syndrome - the reversal of a left-to-right shunt

Definition

- Eisenmenger's syndrome describes the reversal of a left-to-right shunt in a congenital heart defect due to pulmonary hypertension.
- This occurs when an uncorrected left-to-right leads to remodeling of the pulmonary microvasculature, eventually causing obstruction to pulmonary blood and pulmonary hypertension.

Associated with

- ventricular septal defect
 - > Although patients with tetralogy of Fallot have, by definition, a ventricular septal defect they do not go on to develop Eisenmenger's syndrome
- atrial septal defect
- patent ductus arteriosus

Features

- · original murmur may disappear
- cyanosis
- clubbing
- right ventricular failure
- polycythemia
- · haemoptysis, embolism

Management

· heart-lung transplantation is required

Ebstein's anomaly

Definition

 Ebstein's anomaly is a congenital heart defect characterised by low insertion of the tricuspid valve resulting in a large atrium and small ventricle. It is sometimes referred to as 'atrialisation' of the right ventricle.

Causes

Ebstein's anomaly may be caused by exposure to lithium in-utero

Features

- hypoplastic (atrialised) RV,
- apical displacement of the septal and posterior tricuspid valve leaflets,
- ASD
- · Right bundle branch block pattern on ECG.

Associations

- tricuspid incompetence (pan-systolic murmur, giant V waves in JVP)
- Wolff-Parkinson White syndrome occurs in around 15% of the patients.

The presence of delta waves and short PR interval is indicative of WPW. When correlated with past surgical history (repair of atrial septal defect and tricuspid valve abnormalities as a child), Ebstein's anomaly is the most likely diagnosis.

Cardiac manifestations of genetic disorders

Genetic disorder	Associated cardiac manifestation
Marfan's syndrome	Aortic regurgitation (aortic dissection)
Down's syndrome	ASD, VSD
Turner's syndrome	Coarctation of the aorta
Spondyloarthritides, eg, ankylosing spondylitis	Aortic regurgitation

Peripheral vascular disease

- is a marker for increased risk of cardiovascular events even when it is asymptomatic.
- the femoropopliteal artery, the most common site of peripheral arterial disease.
 - ⇒ paresthesia, intermittent claudication in calf and foot and palpable femoral pulses but absent pedal pulses

Risk factors

- age
 - ⇒ about 20% of people aged over 60 years have some degree of peripheral arterial disease.
- · male gender
- Smoking
- Diabetes
- hypertension
- · coronary artery disease.

Feature

- intermittent claudication (leg pain while walking) (The most common initial symptom).
- Critical limb ischaemia: ischaemic pain, ulceration, tissue loss and/or gangrene.

Investigations

- · measuring the ankle brachial pressure index
 - ⇒ Calculate the index in each leg by dividing the highest ankle pressure by the highest arm pressure.
- Imaging before considering revascularization
 - ⇒ duplex ultrasound (first-line imaging)
 - ⇒ contrast-enhanced magnetic resonance angiography (after duplex ultrasound)
 - ⇒ computed tomography angiography (if contrast-enhanced magnetic resonance angiography is contraindicated or not tolerated.)

Treatment

Mild symptoms:

- · exercise programme
 - ⇒ 2 hours of supervised exercise a week for a 3- month period
 - ⇒ encouraging people to exercise to the point of maximal pain.
- management of cardiovascular risk factors (for example, with aspirin or statins)
- vasoactive drug treatment (for example, with naftidrofuryl oxalate).
- Which drug might help improve pain-free walking distance?
 - ⇒ Naftidrofuryl
 - Indicated only when exercise has not led to satisfactory improvement and the person refuse angioplasty or bypass surgery.
 - discontinue naftidrofuryl oxalate if there has been no symptomatic benefit after 3–6 months.
- Vasoactive drugs have limited benefit in treating intermittent claudication.
- There is modest evidence for the use of drugs such as naftidrofuryl and pentoxifylline, but little benefit from cinnarizine or inositol nicotinate.
- Simvastatin may be prescribed for patients with peripheral vascular disease who have elevated cholesterol levels, but there is no data on improvements in walking distance.

severe symptoms:

 endovascular treatment (such as angioplasty or stenting), bypass surgery, pain management and/or amputation.

Differential diagnosis of foot ulcers

	Venous ulcers	Arterial ulcer	Diabetic ulcer Neuropathic ulcer
Location	Gaiter region (above the ankle)	 Pressure points of the foot and shin (e.g., lateral malleolus, tips of the toes) 	 Plantar pressure points of the foot (over the head of the metatarsal bones or the heel)
Mechanism	■ Chronic local venous hypertension → tissue ischemia	 Vessel occlusion → tissue ischemia 	■ Diabetic micro- vasculopathy and neuropathy → impaired tissue sustenance
Wound features	Irregular bordersExudativeSuperficial	Punched-out appearanceNo exudation	Hyperkeratotic bordersDeep
Pain	Mild	Severe	Absent
Additional features	Varicose veinsOedemaStasis dermatitis	 Pale, shiny, cold, hairless surrounding skin Nail dystrophy Absent pulses 	 Charcot joints Absent ankle reflex Impaired sensation (esp. vibration) Claw toes

• Treatment of venous ulceration:

- ⇒ control of oedema, treating any infection, and compression.
- Compressive dressings or devices should not be applied if the arterial circulation is impaired, and ankle-brachial pressure index is needed before application of compression

Rheumatic fever

Definition

• an autoimmune process following infection with group A streptococci.

Overview

- Type <u>II</u> hypersensitivity is seen in rheumatic fever.
- Myocarditis is the most common cause of death during the acute phase of rheumatic fever.

Diagnosis: based on:

- Evidence of recent streptococcal infection accompanied by:
 - 2 major criteria
 - > 1 major with 2 minor criteria
- Evidence of recent streptococcal infection
 - ⇒ ASOT > 200iu/mL
 - ⇒ history of scarlet fever
 - ⇒ positive throat swab
 - ⇒ increase in DNase B titre

Jones Criteria

Rheumatic fever major criteria: J♥NES

- Joints polyarthritis;
- ♥ carditis;
- Nodules (subcutaneous);
- Erythema marginatum;
- Sydenham's chorea.

Major criteria

- 1. erythema marginatum
- 2. Sydenham's chorea
- 3. polyarthritis
- 4. carditis (endo-, myo- or peri-)
- 5. subcutaneous nodules
 - Pea-sized, firm and non-tender.
 - characteristically seen on the extensor surfaces of joints such as knees and elbows and also over the spine.

Minor criteria

- 1. raised ESR or CRP
- 2. pyrexia
- 3. arthralgia (not if arthritis a major criteria)
- 4. prolonged PR interval

Histology

- Aschoff bodies are foci of chronic inflammation seen histologically in the myocarditis of acute rheumatic fever.
 - ⇒ <u>Anitschkow cells</u> are reactive histiocytes with wavy, slender, caterpillar-like nuclei seen in Aschoff bodies of acute rheumatic fever.



Erythematous patches with central clearing

Erythema marginatum

Erythema marginatum is seen in around 10% of children with rheumatic fever. It is rare in adults



Subcutaneous nodules (nodules of rheumatoid arthritis are larger)

Infective endocarditis (IE)

The most common cause of endocarditis:

- Staphylococcus aureus is now the most common cause of infective endocarditis
- *Staphylococcus epidermidis* if < 2 months post valve surgery.

Definition

• an infection of the endocardium, the inner layer of the heart and valves.

Pathophysiology

 Damaged valvular endothelium → adherence of platelets and fibrin → sterile vegetation (microthrombus) → bacteremia → bacterial colonization of vegetation → valve destruction with loss of function

Risk factors

Infective endocarditis - strongest risk factor is previous episode of infective endocarditis

- previous episode of endocarditis: The strongest risk factor for developing infective endocarditis.
- previously normal valves (50%, typically acute presentation)
- rheumatic valve disease (30%)
- prosthetic valves
- congenital heart defects
- intravenous drug users (IVDUs, e.g. Typically causing tricuspid lesion)
- hemodialvsis
- Hypertrophic cardiomyopathy.

Types

Acute Endocarditis	Subacute Endocarditis
Larger vegetations	Smaller vegetations
Attacks previously normal valves	Attacks damaged or abnormal valves
Destructive; 50% mortality rate despite treatment	Less destructive; most patients recover with treatment
High-virulence organisms, especially S aureus	Low-virulence organisms, especially the viridans streptococci <i>S mutans</i> and <i>S sanguinis</i>

The likelihood of infection

- The higher the valvular pressure, the greater the likelihood of infection. Thus, mitral > aortic > tricuspid > pulmonary. The exception to this rule is IV-related infective endocarditis; in this case, the tricuspid valve is the most commonly involved because it is the first valve encountered after venous injection.
- If the valve is already abnormal, then the likelihood of infection is greater and will be most likely on the aortic valve (High-pressure systems create more blood turbulence and permit inoculation of the valve).
- Diseases that affect the mitral valve, such as mitral valve prolapse and mitral regurgitation, are the most common valvular diseases. So the mitral valve is the valve most frequently affected by endocarditis. The exception is IV drug use. In these patients, the tricuspid valve is the most frequently involved valve

Causes

Streptococcus bovis endocarditis is associated with colorectal cancer

- Staphylococcus aureus (coagulase positive): the most common causative organism of IE (especially acute presentation, IVDUs).
 - ⇒ Staphylococcus aureus endocarditis is an aggressive disease frequently associated with valve destruction and abscess formation.
- Staphylococcus epidermidis (coagulase negative) most commonly associated with prosthetic valves < 2 months post operative.
- Streptococcus viridans: commonly causing subacute bacterial endocarditis. The two
 most notable viridans streptococci are Streptococcus mitis and Streptococcus sanguinis.
 They are both commonly found in the mouth and in particular dental plaque so endocarditis
 caused by these organisms is linked with poor dental hygiene or following a dental
 procedure
- Streptococcus gallolyticus (formerly Streptococcus bovis) is associated with colorectal cancer → colonoscopy should be done.
- Bacteroides is the most likely organism following bowel resection, though S. bovis is also seen. Management is metronidazole.
- Candida endocarditis: Risk factors: Intravenous drug abuse, immunodeficiency states and indwelling catheters. The aortic valve is the most common valve to be involved. Treatment with Valve replacement followed by amphotericin B for 6 weeks.
- Non-infective (sterile vegetations)
 - ⇒ systemic lupus erythematosus (Libman-Sacks), commonly result in mitral requrgitation.
 - ⇒ malignancy: marantic endocarditis
- Culture negative causes
 - ⇒ prior antibiotic therapy

- ⇒ Coxiella burnetiid (Q fever agent), typically associated with exposure to animals (sheep and cattle).
- ⇒ Bartonella (from cats)
- ⇒ Brucella
- ⇒ Chlamydia psittaci (from birds).
- ⇒ HACEK: (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)
 - slow-growing, Gram negative bacteria
 - These are normal flora of the upper respiratory tract
 - constitute 5-10% cases of endocarditis:
 - they require prolonged incubation in enriched media and increased carbon dioxide tension.
 - The human bite injury and gram-negative culture make Eikenella corrodens the most likely causative organism.
 - third-generation cephalosporin (Ceftriaxone) is effective against enteric gram-negative rods, including HACEK organisms

Associations	Most common cause
Generally	Staphylococcus aureus
prosthetic valves < 2 months post operative	Staphylococcus epidermidis
IV drug use	Staphylococcus aureus
Recent dental procedure	Streptococcus viridans : (Streptococcus mitis and Streptococcus sanguinis).
Colorectal cancer	Streptococcus gallolyticus (formerly Streptococcus bovis)

Diagnosis

Infective endocarditis: Modified Duke criteria

- Infective endocarditis diagnosed if
 - ⇒ pathological criteria positive, or
 - ⇒ 2 major criteria, or
 - ⇒ 1 major and 3 minor criteria, or
 - ⇒ 5 minor criteria

Pathological criteria

⇒ Positive histology or microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments or intracardiac abscess content)

Major criteria

⇒ Positive blood cultures

- two positive blood cultures showing typical organisms consistent with infective endocarditis, such as Streptococcus viridans and the HACEK group, or
- persistent bacteraemia from two blood cultures taken > 12 hours apart or three or more positive blood cultures where the pathogen is less specific such as Staph aureus and Staph epidermidis, or
- positive serology for Coxiella burnetii, Bartonella species or Chlamydia psittaci, or
- positive molecular assays for specific gene targets

⇒ Evidence of endocardial involvement

 positive echocardiogram (oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves).

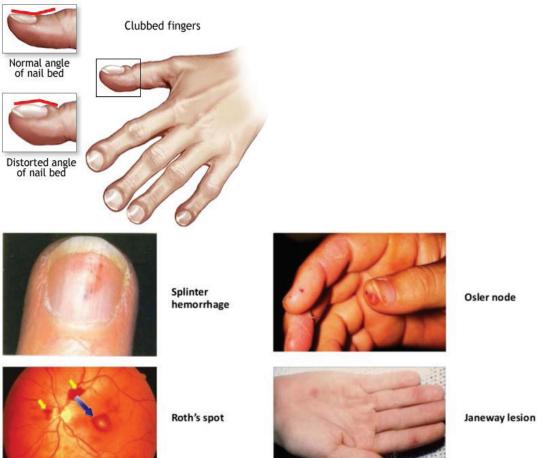
Minor criteria

- 1) predisposing heart condition or intravenous drug use
- 2) microbiological evidence does not meet major criteria
- 3) fever > 38 C
- 4) vascular phenomena: major emboli, splenomegaly, clubbing, splinter haemorrhages, Janeway lesions, petechiae or purpura
- 5) immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots

Classical symptoms of infective endocarditis can be remembered using the mnemonic FROM JANE: fever, Roth spots, Osler nodes, murmur, Janeway lesions, anaemia, nail-bed haemorrhage, emboli.

Ow for Owsler nodes: Osler nodes and Janeway lesions are similar in appearance, yet Osler nodes are painful and Janeway lesions are painless.

Peripheral signs associated with infective endocarditis



Investigation

- Transthoracic echocardiography (TTE) is the initial test of choice for all patients with suspected IE.
- How should the blood samples be drawn to maximise the chances of obtaining positive cultures?
 - ⇒ Draw three samples of blood from different venepuncture sites with the first separated from the last by at least one hour over 24 hours

Aortic valve endocarditis can cause aortic root abscess which can cause damage to the AV node resulting in prolongation of the PR interval on ECG.

Management

Current antibiotic guidelines (source: British National Formulary)

Scenario	Suggested antibiotic therapy	
Initial blind therapy	Native valve:	
Staphylococci endocarditis	Native valve: Not allergic to penicillin , no MRSA , not sever sepsis:	
Streptococci endocarditis	Native valve and Prosthetic valve :	

IV amoxicillin is the empirical treatment of choice in native valve endocarditis

The most useful laboratory test used to monitor the treatment of infective endocarditis is serial C reactive protein estimation.

- · length of treatment:
 - ⇒ 6 weeks of intravenous therapy is generally accepted as the length of treatment needed

Indications for surgery

Infective endocarditis - indications for surgery:

- severe valvular incompetence
- · aortic abscess (often indicated by a lengthening PR interval)
- · infections resistant to antibiotics/fungal infections
- · cardiac failure refractory to standard medical treatment
- recurrent emboli after antibiotic therapy
- organisms that are difficult to eradicate by medical therapy as such fungi, brucella, coxiella, pseudomonas aeruginosa, vancomycin-resistant enterococci
- persistent bacteraemia despite appropriate antibiotic therapy
- extension of infection to a extravalvular site
- early prosthetic valve endocarditis (within 2 months)
- dehiscence or obstruction of a prosthetic valve.
- large (more than 10 mm) vegetations

Prophylaxis

- NICE recommends the following procedures do not require prophylaxis:
 - ⇒ dental procedures
 - ⇒ upper and lower gastrointestinal tract procedures
 - ⇒ genitourinary tract; this includes urological, gynaecological and obstetric procedures and childbirth
 - ⇒ upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy
- Prophylaxis is only recommended in those patients who are at highest risk of adverse outcomes on the development of endocarditis. These patient groups include:
 - ⇒ Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
 - ⇒ Previous endocarditis
 - ⇒ Unrepaired cyanotic congenital heart disease including palliative shunts and conduits
 - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure
 - ⇒ Repaired congenital heart disease with residual defects (persisting leaks or abnormal flow) at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialisation)
 - ⇒ Cardiac transplantation recipients who develop cardiac valve abnormalities.

Prognosis

Infective endocarditis - streptococcal infection carries a good prognosis

Poor prognostic factors

- Staph aureus infection (→ Acute endocarditis)
 - ⇒ (Streptococcus viridans → Subacute bacterial endocarditis has a better prognosis.)
- Prosthetic valve (especially 'early', acquired during surgery)
- · Culture negative endocarditis
- Low complement levels
- Infection of the aortic rather than mitral valve
- Associated rhythm disturbance.
- Heart failure: the most common cause of death from infective endocarditis
- Intravenous drug abuse (often left and right sided disease)
- Old age
- Insulin dependent diabetes mellitus
- Severe co-morbidities.

Mortality according to organism

- Staphylococci 30%
- Bowel organisms 15%
- Streptococci 5%

Myocarditis

The short prodromal illness coupled with the development of biventricular heart failure, tachycardia, T-wave inversion and elevated troponin is most consistent with viral myocarditis. The features, including the mild flu-like illness, are consistent with Coxsackie B.

Pathology

Lymphocytic infiltrate with focal necrosis of myocardial tissue

Causes

- In 50% of cases, no cause can be identified; hence, myocarditis is commonly idiopathic.
- In patients with an identified cause:
 - the most commonly implicated etiology is viral (similar to pericarditis), of which enteroviruses, notably **Coxsackie B**, are the most common.
- Viral:
 - ⇒ The **most common** in adults:
 - Parvovirus B19
 - Human herpes virus 6
 - ⇒ Other Viral Causes
 - Coxsackie B virus
 - most common in children
 - results in <u>dilated</u> cardiomyopathy.
 - Adenovirus, HIV, Hepatitis C, Influenza virus, Epstein-Barr virus
- Bacteria: diphtheria, clostridia
- Spirochaetes: Lyme disease (most commonly presents as heart block).
- protozoa
 - ⇒ Chagas' disease,
 - caused by Trypanosoma cruzi, a common pathogen in South America
 - Chagas disease myocarditis results in <u>dilated</u> cardiomyopathy.
 - ⇒ Toxoplasmosis
 - Noninfectious

- ⇒ Autoimmune (e.g., systemic lupus erythematosus, sarcoidosis, dermatomyositis, polymyositis), Vasculitis (e.g., Kawasaki disease)
- ⇒ Toxins (e.g., carbon monoxide poisoning, black widow venom), Cocaine.
- ⇒ Medication (e.g., sulfonamides), chemotherapy (e.g., anthracycline, doxorubicin)
- ⇒ Radiation therapy

Presentation

- usually young patient with a history of viral prodrome 2 to 3 weeks prior to the onset (fever, arthralgia, myalgia, upper respiratory tract infections)
- typically present with symptoms of heart failure (dyspnea, orthopnea, and leg swelling).
- chest pain, due to involvement of the pericardium.
- Palpitations, typically sinus tachycardia.

Investigations

- Markedly raised troponin.
- ↑ ESR (and CRP)
- ECG:
 - ⇒ sinus tachycardia or ventricular arrhythmias
 - ⇒ nonspecific ST changes
 - ⇒ diffuse ST elevation in those with pericardial involvement (perimyocarditis).
- Echocardiography: global systolic dysfunction

Differential diagnosis

- Acute coronary syndrome
 - ⇒ differentiating factors: ECG changes (NSTEMI and STEMI) with increased troponins

Treatment

- Supportive, usually similar to heart failure.
- NSAIDs should be avoided in the acute phase of acute myocarditis as it may impair healing.

DVLA: cardiovascular disorders

	Group 1	Group 2	
	car and motorcycle	bus and lorry	
Angina	 Must not drive when symptoms occur at rest, with emotion or at the wheel. Need not notify the DVLA. 	 Must not drive and must notify the DVLA when symptoms occur. Driving may be relicensed if no angina for at least 6 weeks. 	
Acute coronary syndromes (ACS)	 After successful coronary angioplasty: can drive after 1 week. If no successful coronary angioplasty, drive after 4 weeks Need not notify the DVLA 	 Can drive after 6 weeks Must notify the DVLA 	
Coronary artery bypass graft (CABG)	Can drive after 4 weeksNeed not notify the DVLA	 Can drive after 3 months Must notify the DVLA 	
Arrhythmia	 Can drive if arrhythmia is controlled for at least 4 weeks. may need to notify the DVLA. 	 Can drive if arrhythmia is controlled for at least 3 months Must notify the DVLA 	
Successful catheter ablation	 May drive after 2 days Need not notify the DVLA 	 For arrhythmia causing incapacity: can drive after 6 weeks. For arrhythmia NOT causing incapacity: can drive after 2 weeks. Must notify the DVLA 	
Pacemaker implant	Can drive after 1 weekNeed not notify the DVLA	Can drive after 6 weeks Must notify the DVLA	
CRT pacemaker	Can drive after 4 weeksMust notify the DVLA	Can drive after 6 weeksMust notify the DVLA	
Implantable cardioverter defibrillator (ICD)	Can drive 6 monthsMay need to notify the DVLA.	Permanent barMust notify the DVLA	
Hypertension	 May drive and need not notify the DVLA 	 Must not drive and must notify the DVLA if resting BP is consistently:180 mm Hg or higher systolic and/or 100 mm Hg or more diastolic. 	
Heart failure	 Asymptomatic: May drive and need not notify the DVLA. Symptomatic: Must not drive but need not notify the DVLA. Left ventricular assist device implanted: Can drive after 3 months. Need not notify the DVLA. 	 Asymptomatic: May drive and need not notify the DVLA. Symptomatic: Must not drive and must notify the DVLA. Relicensing would require LV ejection fraction at least 40% Left ventricular assist device implanted: Licence will be refused permanently. Must notify the DVLA. 	

ICD means:

- · cannot drive a group 1 vehicle for 6 months
- Loss of a group 2 HGV license, regardless of the circumstances

DVLA advice post MI:

- if successfully treated by angioplasty → cannot drive for 1 week
- If does not undergo angioplasty → cannot drive for 4 weeks

DVLA: cardiovascular disorders

Acute coronary syndrome

- if successfully treated by angioplasty → cannot drive for 1 week
- If does not undergo angioplasty → cannot drive for 4 weeks

Coronary artery bypass graft (CABG)

- Group 1 car: 4 weeks off driving
- Group 2 bus and lorry: Must not drive and must notify the DVLA.

pacemaker insertion: 1 week off driving

implantable cardioverter-defibrillator (ICD):

- if implanted for sustained ventricular arrhythmia: cease driving for 6 months.
- If implanted prophylactically then cease driving for 1 month.
- for Group 2 drivers → permanent bar

Heart failure: LVEF of < 40% bars him from driving a lorry, even if he becomes asymptomatic with treatment

successful catheter ablation for an arrhythmia: 2 days off driving

<u>Dextrocardia</u>

Definition

• The heart is located on the right side of the chest.

Epidemiology

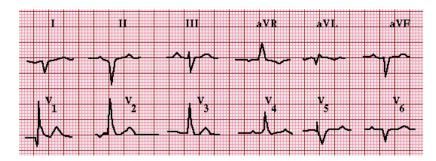
No ethnic or gender-related predilection

Associations

- Situs inversus totalis (reversal in the position of other organs)
- Kartagener syndrome: classic triad of situs inversus (reversal in the position of the abdominal organs), recurrent sinusitis, and bronchiectasis
- When dextrocardia is associated with a normal position of other thoracoabdominal structures, it is called situs solitus.

ECG Features

- Right axis deviation
- Negative P wave and QRS complex in lead I.
- Upright p wave in AVL
- Reverse R wave progression across the precordium; the R wave is tallest in V1 and
 progressively decreases in amplitude in leads V2 to V6. The diagnosis may be confirmed
 by obtaining right-sided chest leads that demonstrate the normal progression of R wave
 amplitude.



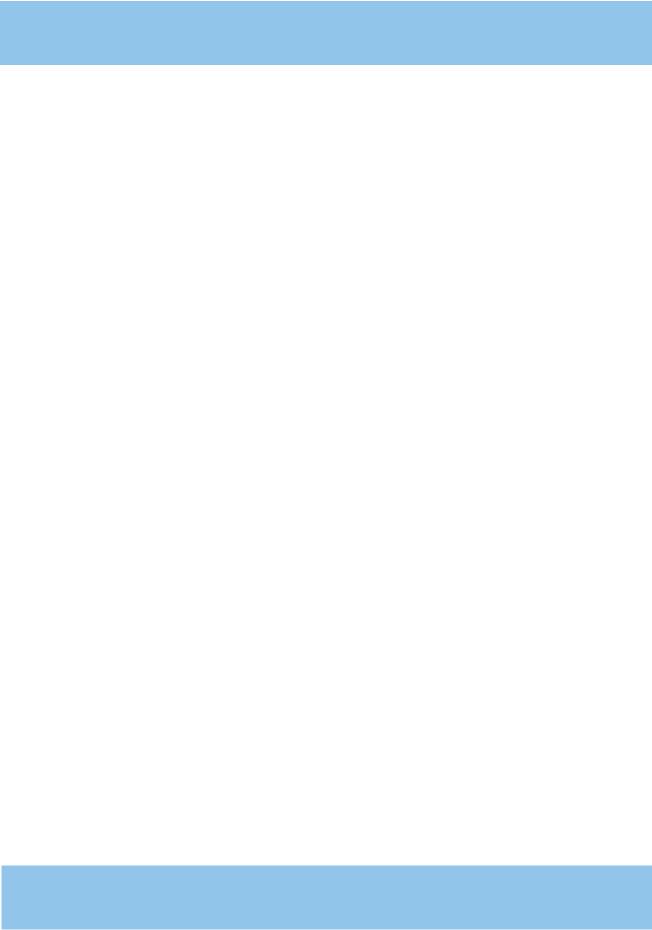
Characteristic changes of dextrocardia include a negative P wave and QRS complex in lead 1, since atrial and ventricular depolarization begin on the left and spread to the right. There is also reverse R wave progression across the precordium; the R wave is tallest in V1, and progressively decreases in amplitude in leads V2 to V6.

Differential diagnosis

- Cardiac dextroposition
 - ⇒ Dextrocardia also involves a change in the orientation of the heart with its base to the apex axis being directed to the right, in contrast to the normal heart orientation where the apex is directed to the left. This change in orientation differentiates it from cardiac dextroposition, where the heart is displaced to the right side as a result of extracardiac causes, such as a diaphragmatic hernia, right pneumonectomy, or right lung hypoplasia.

Prognosis

- Isolated dextrocardia is a benign condition often diagnosed incidentally.
- Typically, patients have a normal life expectancy if no cardiac anomalies are present.



Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Nephrology

Updated 2022

Renal anatomy The tables below show the anatomical relations of the kidneys:

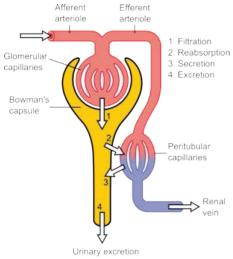
Right kidney

Direct contact	Layer of peritoneum in-between
Right suprarenal gland Duodenum Colon	Liver Distal part of small intestine

Left kidney

Direct contact	Layer of peritoneum in-between	
Left suprarenal gland Pancreas Colon	Stomach Spleen Distal part of small intestine	

Renal physiology



Excretion = Filtration - Reabsorption + Secretion

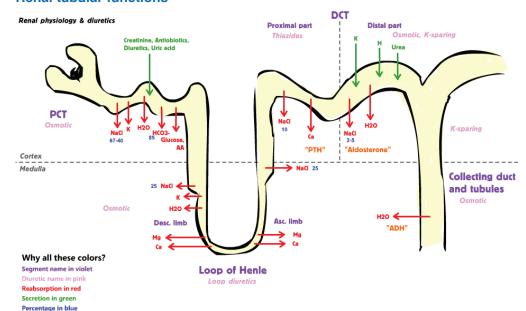
Diagram showing the basic physiologic mechanisms of the kidney

Renal blood flow (RBF)

- Renal blood flow is 20-25% of cardiac output
- The 'Fick principle' can be used to estimate RBF through clearance.
- Sympathetic stimuli produce vasoconstriction and RBF should be increased in response to hypoxia.
- Renal cortical blood flow > medullary blood flow (i.e. tubular cells more prone to ischaemia)
- Glomerular filtration rate and renal blood flow increase by about 50% in pregnancy leading to decreased BUN and creatinine on laboratory examination.
- What is the effect of decrease in hematocrit on renal function?
 - Decreased Renal Blood Flow
 - the relationships between Renal Blood Flow (RBF), Renal Plasma
 Flow (RPF), Hematocrit (Hct), and Glomerular Filtration Rate (GFR):

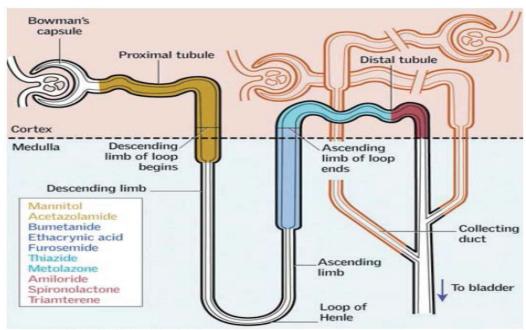
- ❖ RBF = RPF / (1 Hct).
- Assuming that the GFR is stable, this equation suggests that a decrease in Hct would lead to an decrease in RBF.

Renal tubular functions



- Sodium, glucose, bicarbonate and amino acids are absorbed at the proximal tubule level
- Sodium reabsorption is mostly through active transport in the loop of Henle with only a
 modest reabsorption facilitated by aldosterone.
- Ammonia is secreted by the distal tubule
- Regulation of water secretion is by the distal tubule and the collecting ducts under the influence of vasopressin → increase permeability to water.
- The relative hyperosmolality of the medulla is maintained by a counter-current mechanism and is responsible for the flux of water across the renal tubule
- descending loop of Henle is permeable to water but impermeable to solutes, due to the
 presence of aquaporin 1 in its tubular wall → water moves to medullary space → hypertonic
 filtrate
- ascending loop of Henle is impermeable to water (because of a lack of aquaporin, a
 common transporter protein for water channels in all cells except the walls of the ascending
 loop of Henle) but permeable to solutes, but here Na⁺, Cl⁻, and K⁺ are actively transported
 into the medullary space, making the filtrate hypotonic
- What is the renal cellular mechanism that prevents a sodium load intake from drastically increasing plasma osmolality?
 - > Movement of aquaporin channels to the apical surface of collecting duct cells
 - An increase in sodium intake will cause an increase in plasma osmolality, triggering the release of antidiuretic hormone (ADH), a.k.a. vasopressin.
 - ❖ The immediate effect of ADH (occurs over minutes) → movement of aquaporin channels to the apical surface of collecting duct cells.
 - the long-term effect of ADH (occurs over days) →Increase
 in aquaporin gene expression by collecting duct cells.

Hormone in orange



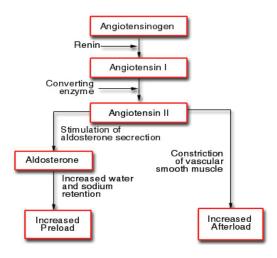
The nephron and sites of action of diuretics.

Renal Physiology of Pregnancy

- Kidneys size increase by 1 to 1.5 cm during pregnancy.
- <u>Kidney volume</u> increases by up to 30%, primarily due to an increase in renal vascular and interstitial volume.
- Glomerular filtration rate (GFR) and renal blood flow rise markedly during pregnancy, resulting in a physiologic fall in the serum creatinine concentration. A serum creatinine of 1.0 mg/dL in a pregnant woman probably reflects significant renal insufficiency.
 - ➤ The glomerular filtration rate **increases** 50% with subsequent **decrease** in serum creatinine, urea, and uric acid values.
- mechanisms contribute to <u>decreased vascular resistance</u>, <u>increased renal plasma flow</u>, and <u>increased GFR</u> during pregnancy:
 - Reduced vascular responsiveness to vasopressors such as angiotensin 2, norepinephrine, and antidiuretic hormone.
 - Additionally, the ovarian hormone and vasodilator relaxin is a key mediator of enhanced nitric oxide signaling in pregnancy.
- The best method to estimate GFR in pregnancy is by 24-hour urine collection for creatinine clearance.
 - Completeness of the collection should be confirmed by checking the 24-hour creatinine excretion (10 to 15 mg creatinine/day per kg body weight is consistent with a complete collection).
 - Estimating equations, such as the Modification of Diet in Renal Disease Study (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, are not accurate in pregnancy.
 - Physiologic <u>ureteral dilatation</u> (hydronephrosis and hydroureter) is common during pregnancy, and results from:

- hormonal effects.
- external compression, and
- intrinsic changes in the ureteral wall.
- Urinary frequency and nocturia are common, but usually require no specific treatment. Urinary incontinence also can occur during pregnancy.
- Other physiologic changes in pregnancy include:
 - respiratory alkalosis,
 - mild hyponatremia,
 - glucosuria, and
 - proteinuria up to 300 mg/day.

Renin-angiotensin -aldosterone system



Renin

- Released by juxtaglomerular cells in kidney in response to ⊥ renal perfusion, low sodium
- Hydrolyses angiotensinogen to form angiotensin I
- when decreased cardiac output occurs, stimulation of renin release is the primary event which leads to peripheral oedema
- renin ↓ in primary hyperaldosteronism due to negative feedback (↑ Aldosterone → ↑ BP
 → ↑renal perfusion → ↓ renin)

Which renal cells would respond first to this acute event of hypotension to increase blood pressure?

Juxtaglomerular cells

Factors stimulating renin secretion

- ↓ BP → ↓ renal perfusion
- Hyponatremia
- renal artery stenosis
- Sympathetic nerve stimulation
- Catecholamines
- Erect posture

Factors reducing renin secretion

- β-blockers
- NSAIDS

Angiotensin

- ACE in lung converts angiotensin I → angiotensin II
- Vasoconstriction leads to raised BP

- Stimulates thirst
- Stimulates aldosterone and ADH

Aldosterone

- Released by the zona glomerulosa (the outer layer of adrenal cortex) in response to raised angiotensin II, potassium, and ACTH levels
- Act in distal tubule → retention of Na+ in exchange for K+/H+ :
 - ↑ resorption of Na+ → ↓Na+ loss in urine
 - → resorption of water (osmotic effect due to ↑ Na+)
 - ↑ excretion of K+

The counter-current concentrating mechanism in the kidney

Urine is concentrated by a complex interaction between the loops of Henle, the medullary interstitium, vasa recta and the collecting tubules, collectively termed 'the counter-current mechanism':

- Vasa recta possess fenestrated walls that facilitate the movement of diffusible substances (free movement of water and electrolytes across the walls of the vasa recta)
- Fine-tuning of the salt and water balance is achieved in the distal and collecting tubules under the influence of aldosterone and antidiuretic hormone
- The ascending limb of the loop of Henle is impermeable to water but permeable to sodium
- All nephrons are involved in this process
- The glomerular filtration rate ensures that the elimination of compounds such as urea from plasma can take place without losing large amounts of water as well

Renal Investigations

<u>Urinalysis</u>

Significance of presence of casts in urine

- Hyaline casts → may be seen in normal urine, particularly after exercise
- Coarse granular casts → occur in glomerular and tubular disease
- Tubular cell casts → may be seen in patients with acute tubular necrosis
- The presence of 10 or more white blood cells/mm3 → infection
- The presence of red-cell casts → characteristic of glomerulonephritis

Red cell casts: Present in:

- Acute glomerulonephritis
- Renal vasculitis

- Accelerated hypertension
- Interstitial nephritis.

Oliquria

- Oliguria is defined as <400 ml urine/day.
- a urine output of <0.5mL/kg/h.

urinalysis	Normal limits	comment
(WBCs) / leukocytes / (pus cells)	< 10	"Significant pyuria " ≥ 10 leucocytes per microlitre (μl) or cubic millimeter (mm³)
dysmorphic RBCs	0 - 3	characteristic of glomerular origin
hemoglobinuria	0	Suggestive of <i>in vivo</i> hemolysis but must be distinguished from hematuria. In case of hemoglobinuria, a urine dipstick shows presence of blood, but no RBCs are seen on microscopic examination.
nitrites	0	a positive test suggests presence of bacteria in significant numbers (ie more than 10,000 per ml), A negative result does not rule out a UTI

Sterile pyuria

Definition

• Pyuria in the absence of bacteriuria

Causes

- adult polycystic kidney disease
- Chemical cystitis (eg cyclophosphamide)
- analgesic nephropathy
- Acute glomerulonephritis
- Tubulo-interstitial diseases

- · partially treated UTI
- urethritis and sexually transmitted diseases e.g. Chlamydia
- · renal tuberculosis
- renal stones
- · foreign body eg: urinary catheter,
- appendicitis
- bladder/renal cell cancer

Glycosuria in pregnancy

- The most likely mechanism of glycosuria in pregnant woman→ Reduced renal reabsorption
- patients with persistent glycosuria should be investigated with a glucose tolerance test at around 24 weeks

Ketonuria in pregnancy

 Ketonuria may also be seen in normal pregnancy, as a result of the increased metabolic requirements

Urine pH

- The range is 4.5 to 8. urine is commonly acidic (ie 5.5-6.5)
- Acidic urine (low pH) may be caused by:
 - diet (eg, acidic fruits such as cranberries)
 - uric acid calculi.
- Urine pH generally reflects the blood pH but in renal tubular acidosis (RTA) this is not the
 case.
 - In type 1 RTA (distal) the urine is acidic but the blood alkaline.

- ➤ In type 2 (proximal) the urine is initially alkaline but becomes more acidic as the disease progresses.
- Alkaline urine (high pH) is seen in:
 - the initial stages of type 2 RTA
 - Infection with urease-splitting organisms,
 - > may be associated with the formation of stag-horn calculi.
 - > Diet, (vegetarians having more alkaline urine when compared with omnivores).
 - Animal proteins contained in meat, eggs and cheese are often converted into
 acidic products (for example, amino acids) during digestion, absorption or
 metabolism. This provides a daily increase in the body's acid content, which has
 to be excreted by the kidneys.
 - For people eating a vegetarian diet, consumption of foods rich in citrate or carbonated drinks raise the urine pH.
 - Other situations can interfere with this balance, such as tubular function or bacterial
 infection, which often promotes an alkaline urine pH due to the presence of bacterial
 enzymes converting urea to ammonia.
 - Effects of urine pH on stone formation:
 - ➤ Acidic urine → uric acid stones are more likely to form.
 - ➤ Alkaline urine → phosphate stones are more likely to form (calcium phosphate becomes less soluble at pH>6;).
 - Excretion of ammonium occurs when an acid urine is produced but the pH of urine is of course determined by the concentration of H+ ions.
 - Unable to lower the pH to less than 5.5 → in type 1 RTA.
 - A pH of above 7.0 after prolonged and severe vomiting would be expected in an attempt
 to compensate for the loss of acid; however, when there is extracellular fluid depletion the
 retention of sodium takes priority. Instead of bicarbonate being excreted it is reabsorbed in
 the proximal and distal nephron and this perpetuates the metabolic alkalosis until the fluid
 balance is restored with intravenous (IV) fluids.

Disproportionately raised creatinine compared with the urea level leads to suspicion of rhabdomyolysis. Additional clue is raised PO4 and K+ & renal failure.

Disproportionately raised urea compared with creatinine level leads to suspicion of dehydration.

Renal investigations

- The most appropriate an urgent scan to exclude obstruction of the kidneys is Ultrasound renal tract
- Retrograde urethro-graphy is the mainstay of investigation for urethral stricture disease
- Renal scintigraphy with DMSA
 - Involves administration of radioactive isotope (dimercaptosuccinic acid) which is taken up by the renal parenchyma.

- This identify regions of decreased uptake due to acute inflammation (such as pyelonephritis) or renal scarring.
- The technique of dimercaptosuccinic acid DMSA scan also allows detection of congenital renal disorder.
- A small kidney with uniform uptake of DMSA is likely to represent congenital hypodysplasia, whereas a focal area of reduced cortical uptake associated with loss of contours is more likely to represent an infection-related scar.

Renal Biopsy

- The hila of the kidneys lie at the L1 and L2 vertebral levels.
- For a routine biopsy there is no preferable side to biopsy, but commonly it is the Lt Kidney.
- Coagulation studies should always be performed prior to renal biopsy due to the risk of bleeding (e.g. in a case of alcohol excess, clotting studies may be deranged).

Complications

- Macroscopic haematuria can occur in up to 10% of renal biopsies.
- Nephrectomy is a rare but serious complication of renal biopsy required to control bleeding.
 It should be consented for that.

Contraindications

- Absolute contraindications to renal biopsy include the following:
 - > Uncorrectable bleeding diathesis
 - > Uncontrollable severe hypertension
 - Active renal or perirenal infection
 - Skin infection at biopsy site
- relative contraindications to renal biopsy:
 - Uncooperative patient
 - > Anatomic abnormalities of the kidney which may increase risk
 - Small kidneys
 - Solitary kidney

Haematuria

- Haematuria is defined as >3 RBC/high power field (hpf) of centrifuged sediment under the microscope.
- Non-visible (Microscopic) haematuria is found in around 2.5% of the population.

Causes of transient or spurious non-visible haematuria

- urinary tract infection
- menstruation
- vigorous exercise (this normally settles after around 3 days)
- sexual intercourse

Causes of persistent non-visible haematuria

- cancer (bladder, renal, prostate)
- stones
- · benign prostatic hyperplasia
- prostatitis
- · urethritis e.g. Chlamydia
- renal causes: IgA nephropathy, thin basement membrane disease

Spurious causes - red/orange urine, where blood is not present on dipstick

- · foods: beetroot, rhubarb
- drugs: rifampicin, doxorubicin

what is the pathophysiology of Exercise-induced hematuria?

- → Extracorpuscular mechanical trauma causing hemolysis
 - patients present after the event with rust-colored urine.

Management

- Current evidence does not support screening for haematuria.
- The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated.

Testing

- urine dipstick is the test of choice for detecting haematuria
- persistent non-visible haematuria is often defined as blood being present in 2 out of 3 samples tested 2-3 weeks apart
- The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin
 to the general population hence these patients should also be investigated as
 normal.
- renal function, albumin: creatinine (ACR) or protein: creatinine ratio (PCR) and blood pressure should also be checked
- urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected
- in an elderly presented with painless macroscopic haematuria. the most important thing to exclude after infection would be a bladder tumour initially before embarking upon a renal biopsy. Therefore cystoscopy is the best initial investigation.

NICE urgent cancer referral quidelines (updated in 2015).

- Urgent referral (i.e. within 2 weeks)
 - Aged ≥ 45 years AND:
 - unexplained visible haematuria without UTI, or
 - visible haematuria that persists or recurs after successful treatment of UTI.
 - ➤ Aged ≥ 60 years AND have unexplained nonvisible haematuria and either dysuria or a raised white cell count on a blood test.
- Non-urgent referral
 - ➤ Aged ≥ 60 years with recurrent or persistent unexplained UTI.
- patients under the age of 40 years with normal renal function, no proteinuria and who are normotensive do not need to be referred and may be managed in primary care.

May 2009 exam: A 62-year-old man with H/O hypertension & AF, on warfarin. A urine dipstick showed blood + with no protein or leucocytes. This result repeated twice. What is the most appropriate action?

→ Cystoscopy (The incidence of non-visible haematuria is similar in patients taking warfarin to the general population therefore these patients should be investigated as normal)

Acute interstitial nephritis (AIN)

Definition

 Acute interstitial nephritis is inflammation of the renal tubulo-interstitium, secondary to a hypersensitivity reaction to drugs.

Epidemiology

accounts for 25% of drug-induced acute renal failure

Pathophysiology

- The onset of AIN occurs approximately 10-14 days after the initiation of the inciting agent and resolves with removal of the offending drug.
- It is typically characterized by Eosinophilia and Eosinophiluria with elevated levels of IgE in the serum suggesting a type I hypersensitivity.
- AIN may also be caused by type IV hypersensitivity with mononuclear interstitial infiltrate on renal biopsy.
- Drug → Hypersensitivity reaction (type IV) within the kidney interstitium → acute kidney injury.

Causes

- Drugs: the most common cause
 - ⇒ NSAIDs, (The most common causative drug)
 - ⇒ Penicillin, rifampicin, cephalosporins, vancomycin, Co-trimoxazole, Sulphonamides
 - ⇒ Allopurinol
 - ⇒ Thiazides and furosemide
 - ⇒ Phenytoin
 - ⇒ Ranitidine, Cimetidine, Omeprazole
- Infection: (eg, Mycoplasma)
- Autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

Features

- Allergic reaction: triad of rash, fever, and eosinophilia (only in 10%)
- Many patients are not oliguric despite moderately severe acute renal failure. Patients with non-oliguric acute renal failure should always be investigated for AIN
- hypertension
- · Proteinuria is dominant

Investigations

- Eosinophilia is common
- Urine: white cells, red cells, and white cell casts (Eosinophiluria)
- Acute Kidney injury (AKI) : ↑ creatinine
- Renal biopsy: for definite diagnosis → shows mononuclear cell infiltrate throughout the interstitium with associated oedema.

Treatment

- . The majority of patients recover following withdrawal of the offending drug
- High-dose prednisolone is indicated in some cases to hasten recovery.
 - ⇒ NSAID-induced AIN does not generally respond to glucocorticoid therapy.
- Dialysis may be required in severe cases.

Prognosis

Good prognosis if it is managed early. Untreated AIN results in interstitial fibrosis.

Drug induced acute interstitial nephritis (AIN)

Remember these 7 P'S:

- 1. Pee drugs (diuretics): Thiazides and furosemide
- 2. Pain-free (NSAIDs)
- 3. Penicillins and cephalosporins
- 4. Proton pump inhibitors
- 5. Phenytoin
- 6. RifamPin
- 7. SulPha drugs: Sulfasalazine, Sulfonylureas

Acute interstitial nephritis (AIN) should be suspected in a patient who presents with an elevated serum creatinine and a urinalysis that shows white cells, white cell casts, and, in some cases, eosinophiluria.

Contrast induced acute kidney injury (CI- AKI)

Definition

- a 25% increase in creatinine occurring within 3 days of the intravascular administration of contrast media. eg: iv contrast agent during angiography
- A continued enhancement of the kidneys days after contrast injection suggests contrastinduced nephropathy.

Features

- ↑ serum creatinine within 24 to 48 hours after the iodinated contrast exposure (usually mild)
 - ⇒ Patients with **oliguria** and **severe AKI** (who may require renal replacement therapy) may be more likely to have an alternate etiology of AKI.
- Most patients are nonoliguric. Oliguria may develop in patients with severe AKI and in
 patients with moderate to severe chronic kidney disease (CKD) at baseline.
- **Protein excretion is typically absent or mild** (unless the patient had proteinuric CKD at baseline).
- Urine: usually shows classic findings of acute tubular necrosis (ATN), including muddy brown granular and epithelial cell casts and free renal tubular epithelial cells

Risk of acute kidney injury in adults having iodine-based contrast media

- chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m2 are at particular risk)
- diabetes but only with chronic kidney disease (adults with an eGFR less than 40 ml/min/1.73 m2 are at particular risk)
- heart failure
- renal transplant
- age 75 years or over
- hypovolaemia
- increasing volume of contrast agent
- intra-arterial administration of contrast medium with first-pass renal exposure (when the contrast reaches the renal arteries in a relatively undiluted form, e.g., through injection into the left heart, thoracic and suprarenal abdominal aorta, or the renal arteries.).

Preventing acute kidney injury in adults having iodine-based contrast media

- Adequate hydration is the most important step to prevent contrast media nephropathy → (iv 0.9% sodium chloride or isotonic sodium bicarbonate)
- Temporarily stop ACE inhibitors and ARBs if eGFR < 40 ml/min/1.73 m²
- . Metformin is usually withheld for 48 hours after the use of contrast

Criteria for renal replacement therapy in AKI

- if any of the following are not responding to medical management:
 - ⇒ hyperkalaemia
 - ⇒ metabolic acidosis
 - ⇒ symptoms or complications of uraemia (for example, pericarditis or encephalopathy)

 - ⇒ pulmonary oedema.

Imaging for Dialysis-dependent patients

- Dialysis-dependent patients who receive contrast for a CT scan may need haemodialysis to remove the contrast.
- MR contrast tends not to be nephrotoxic and therefore haemodialysis is not usually necessary to remove MR contrast.
- The magnetic resonance angiography with gadolinium is not recommended because it carries a risk of nephrogenic systemic fibrosis

MRCP-part-1- exam- January 2014 exam: What is the most important step in reducing the risk of contrast-induced nephropathy?

→ Intravenous 0.9% sodium chloride pre- and post-procedure

Acute tubular necrosis vs. prerenal uraemia

ATN or prerenal uraemia? In prerenal uraemia think of the kidneys holding on to sodium to preserve volume

	Pre-renal uraemia	Acute tubular necrosis
Pathology	due to hypoperfusion due to circulatory co and/or nephrotoxins	
Urine sodium	< 20 mmol/L	> 30 mmol/L
Urine osmolality	>500	<350
Fractional sodium excretion*	< 1%	> 1%
Fractional urea excretion**	< 35%	>35%
Urine: plasma osmolality	> 1.5	< 1.1
Urine: plasma urea	> 10:1	< 8:1
urine/plasma creatinine	>40	<20
Specific gravity	> 1020	< 1010
Urine	'bland' sediment A urine free of red blood cells or casts	brown granular casts
Response to fluid challenge	Yes	No

- *fractional sodium excretion = (urine sodium/plasma sodium) / (urine creatinine/plasma creatinine) x
 100
- **fractional urea excretion = (urine urea /blood urea) / (urine creatinine/plasma creatinine) x 100
- 80-90% Of the acute renal failure seen by physicians will fall into the category of prerenal failure or ATN.
- Normal plasma osmolality = 278 305 mOsmol/Kg
- Normal urinary osmolality = 350 1000 mOsmol/Kg

September 2009 exam: Which test is most useful when determining whether there is prerenal uraemia or acute tubular necrosis?

→ Urinary sodium

Acute tubular necrosis (ATN)

Pathological mechanism

- ATN usually arises following an acute ischaemic or nephrotoxic event
 - ⇒ in ischemic causes of ATN → the thick ascending limb of the Loop of Henle is injured
 - ⇒ in nephrotoxic event → the proximal convoluted tubule is affected.
- the injured tubular cells fail to reabsorb sodium, tubular concentrating ability is lost, and urea clearance is low

Causes of ATN include

- Hypotension
- Hypertension: Accelerated hypertension can cause small vessel obstruction with proliferative endarteritis of intralobular arteries and fibrinoid necrosis of afferent arterioles and glomerular capillary tuft.
- Rhabdomyolysis
- Hepatic failure: Renal failure from ATN occurs in 25% of patients with severe hepatic damage.
- Eclampsia
- Drugs such as:
 - aminoglycosides,
 - Aminoglycoside undergoes glomerular filtration and then reabsorption in the proximal tubule where tubular cell injury/death occurs.
 - > cephalosporins,
 - cisplatin,
 - amphotericin.
 - Heavy metal poisoning, carbon tetrachloride,
 - Heroin addicts. Associated furosemide is likely to increase the plasma concentration of toxic drugs and leads to (ATN).
 - Corticosteroid therapy has not been associated with ATN.

Phases: (ATN) is characterised by 3 phases:

- 1. Initiation phase, with acute decrease in GFR with sudden rise in serum creatinine \pm oliguria
- 2. **Maintenance phase**, with a sustained marked reduction in GFR and rising Cr (1-2 weeks)
- 3. **Recovery phase**, in which tubular function is gradually restored and urine volume gradually rises, with concomitant decrease in Cr to pre-injury levels

Features

- Oliguria is common in the early stages of acute tubular necrosis (ATN)
- ATN after aminoglycoside → impairment in the concentrating ability, and most patients are non-oliguric
- acute renal failure expected to begin more than five days after the initiation of gentamicin
- Small amounts of 'tubular' proteinuria (<1 g/day) may be seen, but >3 g suggests a glomerular leak
- Urinalysis often reveals brown granular casts, which are tubular epithelial cells.

Precautions in management

- After inappropriate attempts to initiate a diuresis by infusion of normal saline without adequate monitoring of the patient's volume status, pulmonary oedema due to salt and water retention is not uncommon
- Aminoglycoside nephrotoxicity correlates with→ Frequency of aminoglycoside dosing

 Multiple human clinical trials (including meta-analysis) studies report less nephrotoxicity and equal efficacy when aminoglycosides are given once daily (supratherapeutic doses) rather than in conventional divided doses.

Prognosis

- Oliguria during the initial stages of ATN is followed by polyuria, and even after a relatively minor insult, recovery may take up to 6 weeks
- Creatinine clearance would be expected to be normal in only 40% of cases one year after the initial insult.
- The mortality rate associated with ATN may be up to 50%, but this is largely dependent on the precipitating illness
- the chance of recovery of renal function to the level where dialysis is not required > 95 %

Complication

- Sepsis, particularly Gram-negative septicaemia, is the most frequent complication and cause of death in acute renal tubular necrosis while awaiting spontaneous recovery of renal function
 - Neither the use of prophylactic antibiotics nor barrier nursing has been shown to reduce infection risk in this situation.

Papillary necrosis

Causes

- chronic analgesia use (concomitant diuretic use may exacerbate renal hypotension)
- sickle cell disease
- TB
- acute pyelonephritis
- · diabetes mellitus
 - UTI are relatively more common in women with diabetes. Untreated infections in people with diabetes can result in renal papillary necrosis,

Features

- fever, loin pain, haematuria
- IVU papillary necrosis with renal scarring 'cup & spill'

Consequences of renal papillary necrosis

· Ureteric obstruction may result if the papillae have sloughed off

Management

- Where there is obstruction, → review by a urologist is advised as ureteric stent placement may be required
- If there is no obstruction → withdrawal of the offending agent + adequate hydration

Acute Pyelonephritis

Epidemiology

 The two peaks of incidence in adults occur in young sexually active women and in men > 50 years of age

Aetiology

- Gram-negative bacilli such as Escherichia coli or Klebsiella species are responsible in more than 95% of cases
- Unusual organisms may be responsible if there has been a history of urethral instrumentation

- Staphylococcal urinary sepsis is usually indicative of haematological seeding of infection Symptoms
 - include fever, rigors, flank pain, dysuria, polyuria, haematuria, nausea and vomiting, headache and diarrhea. The absence of fever rules out acute pyelonephritis

Investigations

- In young women with a first infection, urine culture may be all that is required
- urea and electrolytes measurement, a full blood count and blood cultures, and renal ultrasound in compromised patients

Treatment

- trimethoprim or ciprofloxacin
- Surgical opinion may be required for:
 - > recurrent infections
 - > evidence of vesicoureteric reflux on scanning.

Acute vs. chronic renal failure

Best way to differentiate is renal ultrasound - most patients with CRF have bilateral small kidneys. (normal range for both kidneys 10-12 cm)

Renal size

Renal size asymmetry in the presence of hypertension and renal impairment suggest renovascular disease.

Small kidneys suggest chronic renal failure

The usual range of kidney size measured longitudinally is between 9-12 cm.

Causes of Large kidneys → (chronic renal failure with normal/enlarged kidneys)

- amyloidosis
- Stage 1 diabetic nephropathy
- Hydronephrosis
- Rapidly progressive glomerulonephritis
- HIV-associated nephropathy

- Acromegaly
- Renal vein thrombosis
- Adult polycystic kidney disease
- Scleroderma

Causes of one small kidney

- Renal arterial disease

Other features suggesting CRF rather than ARF

- hypocalcaemia (due to lack of vitamin D)
- evidence of renal osteodystrophy on plain X-ray
- skin pigmentation and peripheral neuropathy are the result of long-standing metabolic abnormality such as chronic renal failure

Cholesterol embolization

Overview

- · cholesterol emboli may break off causing renal disease
- · seen more commonly in arteriopaths, abdominal aortic aneurysms

Features

- eosinophilia
- purpura

- renal failure
- livedo reticularis

MRCPUK-part-1-May 2014 exam: H /O impaired RFT + purpuric rash on feet after coronary angiogram is performed for acute MI. What is the most likely diagnosis?

→ Cholesterol embolization (Cholesterol embolisation is a well-documented complication of coronary angiography)

Chronic kidney disease (CKD)

Definition

Impaired renal function for >3 months based on abnormal structure or function, (GFR < 60 mL/minute/1.73 m²)

Common causes

- diabetic nephropathy (Type II > type I)
- hypertension
- chronic glomerulonephritis (commonly IgA nephropathy)
- · chronic pyelonephritis
- · adult polycystic kidney disease

Investigations

- Creatinine-based estimate of glomerular filtration rate (eGFR)
 - ⇒ If eGFR result is less than 60 ml/min/1.73 m² in a person not previously tested, what is the next step → Repeat the test within 2 weeks.
 - ⇒ The most commonly used formula now is the CKD-EPI equation (more accurate than the old MDRD equation), which uses the 4 variables: serum **c**reatinine, **a**ge, **g**ender and **e**thnicity.
 - ⇒ The new 2021 version of CKD-EPI equation does **not** include a term for race.
 - ⇒ Factors, which may affect the result
 - muscle mass ↓muscle mass (e.g. amputees, body-builders) → overestimation. ↑ muscle mass → underestimation.
 - eating red meat 12 hours prior to the sample being taken
 - pregnancy
- Urine albumin to creatinine ratio (ACR): the first initial test for Albuminuria
- ⇒ ACR > 30 mg/g indicates albuminuria
- ⇒ If ACR 30 70 mg/mmol → repeat with early morning sample to confirm
- ⇒ If ACR ≥70 mg/mmol → no need to repeat
- Urine for haematuria
- ⇒ Diagnosed by reagent strips , no need to use urine microscopy to confirm
- · Renal doppler ultrasound
- ⇒ the first-line imaging technique for the assessment of kidney structure.
- ⇒ Helps to diagnose CKD if kidney atrophy is present

Creatinine-based estimate of GFR VS Cystatin C-based estimate of GFR

- There are no difference in the bias between the equations,
- Precision may be worse with cystatin C-based estimates.
- Creatinine-based estimate of GFR are recommended by NICE as initial first choice
- When to use a cystatin C-based estimate of GFR for diagnosis of CKD? (Nice 2014)
 - ⇒ If creatinine based eGFR is 45–59 ml/min/1.73 m2, sustained for at least 90 days + no proteinuria or other marker of CKD → do eGFR cystatin C, if it is more than 60 ml/min/1.73 m2 → rule out CKD

Creatinine-based estimate of glomerular filtration rate (eGFR)

- 2 formulas are used
 - ⇒ Modification of Diet in Renal Disease (MDRD) equation
 - Uses the 4 variables: serum creatinine, age, gender and ethnicity.
 - Paradoxical higher risk observed in people at higher eGFR
 - Performs better at lower levels of GFR
 - ⇒ CKD-EPI equation
 - more accurate than MDRD equation
 - Less bias at eGFR > 60, similar performance at eGFR < 60.
 - Recommended now as the best equation
 - The new version (2021) of this equation does not include a term for race

Classification of CKD

Stage	Description	eGFR (ml/min)	Notes
1	Normal	>90	with other evidence of chronic
			kidney damage e.g. Albuminuria
2	Mild impairment	60-89	with other evidence of chronic
			kidney damage
3a	Moderate	45-59	with or without evidence of
	impairment		chronic kidney damage
3b	Moderate	30-44	with or without evidence of
	impairment		chronic kidney damage
4	Severe impairment	15-29	with or without evidence of
			chronic kidney damage
5	End stage renal	Less than 15	or on dialysis
	failure (ESRF)		

Features

- Early stages are often asymptomatic
- Symptoms usually only occur once stage 4 is reached (GFR <30).
- Symptoms of end-stage renal disease (eg, pruritus, refractory electrolyte imbalances, metabolic acidosis, severe nausea, neurologic impairments) typically occur when GFR is 5 to 10 mL/minute/1.73 m²

Consequences of CKD

- Hyperkalaemia
 - \Rightarrow CKD \rightarrow metabolic acidosis \rightarrow causes the ion to exit the intracellular space to the extracellular $\rightarrow \uparrow \uparrow$ serum potassium
 - ⇒ CKD → decreased potassium excretion
- Hyperphosphataemia : CKD → ↓ phosphate excretion → ↑ hyperphosphatemia.
- Secondary Hyperparathyroidism: ↓ Ca²⁺ + ↑ serum phosphate → ↑ PTH
- Metabolic acidosis is a result of bicarbonate wasting and reduced ammonia and acid excretion.
- Hypertension: due to sodium and water overload and direct renal effects secondary to the underlying renal disease.
- Anaemia
 - due to decreased erythropoietin production, low grade haemolysis, inadequate intake
 - \Rightarrow \downarrow synthesis of erythropoietin \rightarrow \downarrow stimulation of RBC production \rightarrow normocytic, normochromic anemia
- Hypertriglyceridaemia
 - ⇒ Due to decreased plasma lipoprotein lipase activity
- Pericarditis and cardiomyopathy
 - uraemia leads to exudation of fibrin onto the epicardial and pericardial surfaces.
- Glucose intolerance: due to tissue insulin resistance.
- Cardiovascular-associated CKD-complications
- Increased risk of vascular diseases:
 - ⇒ Increased risk of coronary artery disease and stroke
 - ⇒ A falling GFR is an *independent risk* factor for cardiovascular disease → *this is* the chief cause of death from renal failure.
- Increased skin pigmentation

<u>Chronic kidney disease (CKD): Disorders of mineral and bone metabolism</u>

Hypocalcaemia

- Secondary to reduced levels of 1,25(OH)₂ vitamin D
 - \Rightarrow \downarrow Renal hydroxylation of vitamin D \rightarrow \downarrow 1,25-(OH)2 vitamin D3 \rightarrow \downarrow intestinal Ca2+ absorption \rightarrow \downarrow Ca2+
- Secondary to hyperphosphataemia
 - \Rightarrow \downarrow Renal excretion of phosphate \rightarrow hyperphosphatemia \rightarrow calcium-phosphate precipitation in tissues \rightarrow \downarrow Ca2+

Hyperphosphataemia PO(4) ↑↑: Due to reduced phosphate excretion.

Secondary hyperparathyroidism

hyperphosphataemia and hypocalcaemia → ↑↑ parathyroid hormone (secondary hyperparathyroidism) → renal osteodystrophy.

Renal osteodystrophy

- Definition: Renal osteodystrophy refers to specific changes in bone morphology
 associated with CKD. The term "renal osteodystrophy" is exclusively used to define bone
 pathology observed on biopsy.
- Diagnosis
 - ⇒ PTH is the best noninvasive test for the assessment of bone turnover.
 - Bone biopsy is the gold standard for diagnosing renal osteodystrophy and identifying the specific type.
- **Subtypes** include osteitis fibrosa cystica, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy (MUO).
 - ⇒ Osteitis fibrosa cystica
 - characterized by high bone turnover due to persistently high PTH.
 - There is a marked increase in the number and activity of osteoblasts (ie, bone-forming cells) and osteoclasts (bone-reabsorbing cells) and an increase in osteoid (unmineralized bone).
 - PTH >450 pg/mL suggests osteitis fibrosa cystica

⇒ Adynamic bone disease

- most common form of renal osteodystrophy observed in dialysis patients, particularly diabetic patients.
- characterized by low bone turnover with reductions in both osteoblast and osteoclast activity.
- Risk factors include the use of calcium-containing phosphate binders, highdialysate calcium, and the use of active vitamin D analogs.
- Features: usually asymptomatic, bone pain.
- Complications: fractures, hypercalcemia, and vascular calcification
- Suggested diagnosis among dialysis patients →very↓↓ (PTH; ie, <100 pg/mL) especially if hypercalcemia is present.
- Suggested diagnosis among patients who are not on dialysis →Initially high PTH and progressively ↓↓ less than normal during treatment with vitamin D analogs.
- normal or low bone-specific alkaline phosphatase (BSAP)
- Treatment: by allowing PTH secretion to rise.
 - using non-calcium-containing phosphate binders rather than calciumcontaining phosphate binders
 - decrease the dose or stop calcitriol and all active vitamin D analogs
 - For dialysis patients → use low-calcium dialysate (ie, 2 mEq/L) rather than standard (ie, 2.5 mEq/L)

⇒ Osteomalacia

- characterized by decreased mineralization, causing an increase in unmineralized osteoid
- caused by aluminum deposition in bone.
- uncommon in ESKD patients since aluminum-based phosphate binders were abandoned

Extra-skeletal calcification (Metastatic calcification)

- mainly due to calcium phosphate deposition,
- Increased prevalence with time on haemodialysis
- CKD managed with dialysis is the commonest cause of secondary oxalosis (acute arthritis
 of small joints with digital calcific deposits).
- Calciphylaxis: a rare complication of end-stage renal failure.
 - ⇒ **Pathophysiology:** deposition of calcium within arterioles causing microvascular occlusion and necrosis of the supplied tissue.

- ⇒ Features: most commonly affects the skin and presents with painful necrotic skin lesions.
- ⇒ **Risk factors**: hypercalcaemia, hyperphophataemia and hyperparathyroidism.
- ⇒ **Exacerbating factors:** Warfarin is widely reported as causing/exacerbating calciphylaxis in high risk patients, however the underlying mechanism is not known.
- ⇒ Treatment:
 - reducing calcium and phosphate levels and controlling hyperparathyroidism
 - avoiding contributing drugs such as warfarin and calcium containing compounds.

Management

- · Reduce hyperphosphataemia
 - ⇒ Phosphate binders
 - 1st line: calcium based binders such as <u>calcium acetate</u> is the most appropriate initial treatment. the additional calcium in calcium acetate may be sufficient to increase the plasma calcium into the normal range. Side effects: vascular calcification
 - 2nd line: if calcium acetate is not indicated (eg, hypercalcaemia or low serum parathyroid hormone levels) or not tolerated → Offer sevelamer carbonate
 - aluminium containing binders are no longer used
 - ⇒ Dialysis
 - Dialysis is able to remove only about half of the phosphate that the healthy kidney would be able to do. The healthy adult kidney excretes 5400 mg per week of phosphate. the maximum amount of phosphate that can be removed by dialysis in a patient with anuric renal failure who is dialysis dependent is 2700 mg / week.
- Reduce PTH level → vitamin D

chronic renal failure and hypocalcaemia with a raised parathyroid hormone (PTH) \rightarrow secondary hyperparathyroidism.

Chronic renal failure leads to hyperphosphataemia, which triggers release of parathyroid hormone.

Studies such as UKPDS reveal that:

- improving **glycaemic control** would reduce <u>microvascular</u> complications but this has no significant impact upon cardiovascular morbidity and mortality.
- lowering blood pressure significantly reduced morbidity from both microvascular and macrovascular disease.

CKD: only diagnose stages 1 & 2 if supporting evidence to accompany eGFR

eGFR variables => CAGE => Creatinine, Age, Gender, Ethnicity

MRCPUK-part-1-January 2010 exam: Which factor is most likely to invalidate the use of the Modification of Diet in Renal Disease (MDRD) equation to calculate a patients eGFR?

→ Pregnancy

MRCPUK-part-1-May 2012 exam: Which factor is most likely to explain unexpectedly low result of eGFR?

→ Large muscle mass secondary to body building

Diabetic nephropathy

Definition

 Persistent albuminuria due to glomerular injury that is caused by prolonged exposure to hyperglycemia

Epidemiology

- Diabetic nephropathy is a major cause of end stage renal disease (ESRD).
- The peak incidence of frank albuminuria is 17 years after diagnosis of type 1 diabetes

Pathophysiology

- Seen in patients with diabetes for > 10 years
- Glomerulosclerosis the most common renal complication of DM
- The characteristic microscopic changes which will confirm a diagnosis of diabetic nephropathy
 - **⇒** Focal nodular mesangial tissue expansion
 - **⇒ Kimmelstiel-Wilson lesion** → Pathognomonic nodular glomerulosclerosis

Risk factors

Modifiable	Non-modifiable	
Hypertension Hyperlipidaemia	Male sex Duration of diabetes	
SmokingPoor glycaemic controlRaised dietary protein	Genetic predisposition (e.g. ACE gene polymorphisms)	

Stages

Stage	Description
Stage 1	hyperfiltration: increase in GFRmay be reversible
Stage 2 (silent or latent phase)	 most patients do not develop microalbuminuria for 10 years GFR remains elevated
Stage 3 (incipient nephropathy)	microalbuminuria (albumin excretion of 30 - 300 mg/day, dipstick negative)
Stage 4 (overt nephropathy)	 persistent proteinuria (albumin excretion > 300 mg/day, dipstick positive) hypertension is present in most patients histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules)
Stage 5	end-stage renal disease, GFR typically < 10ml/minrenal replacement therapy needed

Diagnosis

- Microalbuminuria is the earliest clinical sign of diabetic nephropathy.
- Urinary albumin to creatinine ratio ≥ 30 mg/g, GFR < 60 mL/minute/1.73 m²
 - ⇒ Absence of albuminuria in patients with diabetes and a reduced estimated GFR raises the possibility of nondiabetic chronic kidney disease

Management

- Optimal glycaemic and blood pressure control
 - ⇒ BP control: aim for < 130/80 mmHg
 - ⇒ Early antihypertensive treatment delays the progression of diabetic nephropathy.
 - ⇒ ACE inhibitors or angiotensin receptor blockers, are the preferred drugs

The best therapeutic option to prevent progression of renal disease → Treat with ACEI (superior to glycaemic control)

CKD: anaemia

Causes of anaemia in renal failure

reduced erythropoietin levels - the most significant factor

Investigations: diagnostic tests

- Hypochromic red blood cells content (% HRC; > 6%)
- If using % HRC is not possible, use reticulocyte Hb content (CHr; < 29 pg)
- If % HRC & CHr are not available, use Combination of transferrin saturation (< 20%) and serum ferritin measurement (<100 micrograms/litre).

Management

- 1st step: correct iron status with oral or iv
 - ⇒ Most non haemodialysis patient may take oral iron . In contrast most haemodialysis patients will require intravenous iron
 - ⇒ **Transfusions in patients awaiting renal transplants** are usually avoided where possible, due to the potential risk of circulating antibodies and thus organ rejection.

- If the patient is haemodynamically unstable and an urgent blood transfusion is advised (e.g. symptoms and signs of severe anaemia, i.e. angina): → postpone transplant for at least 3 months, following repeat antibody screening.
- **2**nd **step:** Once iron stores are restored and ferritin is in the normal range, if the patient is still anaemic then erythropoietin would be the next appropriate option
- Targets for treatment
 - ⇒ **Hb**: **10 12 g/dl** (NICE 2015)
 - Ferritin: 200-500 μg/L (NICE 2015 advice: ferritin should not rise > 800 mic/litre & review iron dose when ferritin reach 500.
 - ⇒ Transferrin saturation >20%
 - ⇒ haematocrit <33%.
 </p>
 - ⇒ percentage hypochromic red cells <6%.

Current Renal Association guidelines suggest that the target Hb for <u>patients receiving</u> erythropoetin therapy is between 105-125 g/L.

CKD - Management

Referral criteria for specialist assessment

- Risk of needing renal replacement therapy
- ACR ≥ 70 mg/mmol (unless diabetic)
- ACR >30 mg/mmol + haematuria
- ↓↓ eGFR ≥ 25% and a change in eGFR category within 12 months
- ↓↓ eGFR ≥ 15 ml/min/1.73 m² per year
- Poorly controlled hypertension despite the use of at least 4 antihypertensive medicines
- Suspected renal artery stenosis or genetic causes of CKD

Chronic Kidney Disease CKD: management of hypertension

- Hypertension is both a cause and consequence of chronic kidney disease.
- Treatment
 - ⇒ Angiotensin-receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor: the 1st line for CKD + ACR > 30.
 - Side effects: NICE suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable. A rise greater than this may indicate underlying renovascular disease.
 - ⇒ Furosemide is useful as anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min*.(*the NKF K/DOQI guidelines suggest a lower cutoff of less than 30 ml/min)
- Target range for BP in CKD: NICE guidelines recommend that:
 - \Rightarrow CKD + proteinuria ACR <70 mg/mmol \rightarrow < 140/90 (target range 120-139/<90).
 - ⇒ CKD + proteinuria ACR ≥70 mg/mmol or DM → < 130/80 (target range 120-129/<80).
 </p>

Chronic Kidney Disease : Diagnosis and management of proteinuria

- **Diagnosis**: Proteinuria (ACR ≥ 3 mg/mmol)
 - ⇒ Urine reagent strips are not used
 - ⇒ Urine Albumin: creatinine ratio (ACR) is the first initial test

- If ACR 3 70 mg/mmol → repeat with early morning sample to confirm
- If ACR ≥70 mg/mmol → no need to repeat
- ⇒ in non-diabetics an ACR greater than 30 mg/mmol is considered clinically significant proteinuria
- ⇒ in **diabetics** microalbuminuria (ACR greater than 2.5 mg/mmol in men and ACR greater than 3.5 mg/mmol in women) is considered clinically significant.

Management

- ⇒ CKD + DM + ACR ≥ 3 mg/mmol → ARB or an ACE inhibitor
- ⇒ CKD without diabetes + ACR ≥ 70 mg/mmol → ARB or an ACE inhibitor & nephrologist assessment
- ⇒ CKD without diabetes + ACR above 30 but below 70 mg/mmol → monitor
- ⇒ Spironolactone
 - The second choice to reduce proteinuria after ACEi
 - Side effects: hyperkalaemia & small ↓ in GFR

Effects of ARB or ACE inhibitor on CKD

- III proteinuria & BP
- 11 breakdown of bradykinin (an efferent arteriolar vasodilator);
- \pmp production of cytokines, such as transforming growth factor-beta (TGF-beta), that promote glomerulosclerosis and fibrosis.

ARB or ACE inhibitor in CKD (NICE guidelines/ November 2021)

- Monitor serum potassium before starting and 1 and 2 weeks after starting or increasing the dose.
 - ⇒ If potassium > 5.0 mmol/litre : do not start
 - ⇒ If potassium ≥ 6.0 mmol/litre: **stop** ARB or an ACE inhibitor
- Monitor eGFR before starting and 1 and 2 weeks after starting or increasing the dose.
 - ⇒ If eGFR ↓↓ by < 25% or serum creatinine ↑↑ by < 30% of baseline: do not modify the dose and repeat the test in 1 to 2 weeks.
 </p>
 - ⇒ If eGFR ↓↓ by ≥ 25%, or serum creatinine ↑↑ by ≥ 30%: look for other causes (e.g., NSAIDs), stop or reduce the dose and add an alternative antihypertensive if needed.

Prescribing in patients with renal failure

Questions regarding which drugs to avoid in renal failure are common

Drugs to avoid in renal failure

- antibiotics: tetracycline, nitrofurantoin
- NSAIDs
 - NSAIDs reduce glomerular perfusion by inhibiting production of prostaglandins which dilate the afferent arteriole of the glomerulus. The reduction in blood supply to the kidney results in impairment of kidney function.
 - > Thus, the most likely cause of renal decline is prostaglandin related.
 - NSAIDs can also cause an interstitial nephritis but this is often accompanied by a nephrotic syndrome-like picture.

- lithium
- metformin

Drugs likely to accumulate in chronic kidney disease - need dose adjustment

- · most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- digoxin, atenolol
- methotrexate
- sulphonylureas
- furosemide
- opioids
 - Alfentanil, buprenorphine and fentanyl are the preferred opioids in patients with chronic kidney disease.

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin
- Omeprazole is principally dependent upon hepatic clearance and safe even with marked renal impairment.

•

Erythropoietin

 Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes.

Sources of Erythropoietin

- interstitial fibroblasts in the kidney (predominant during adulthood)
- perisinusoidal cells in the liver (predominates in the fetal period)
- Exogenous erythropoietin, or recombinant human erythropoietin (rhEPO), is produced by recombinant DNA technology .

The main uses of erythropoietin are

- to treat the anaemia associated with chronic kidney disease
 - > The best option to relieve fatigue in patient with end stage renal failure is Treatment of anaemia with erythropoietin
 - ➤ Improvement in haemoglobin level results in the increased well-being and better appetite.
- Anaemia associated with cytotoxic therapy.
- Prevention of anaemia in premature babies with low birth weight.

Side effects of erythropoietin

- accelerated hypertension → headache, encephalopathy & seizures (BP ↑↑ in 25%)
- · ischaemic stroke
- bone aches
- flu-like symptoms
- skin rashes, urticaria
- pure red cell aplasia (PRCA)

- raised PCV thrombocythaemia → ↑ risk of thrombosis (e.g. Fistula)
- iron deficiency 2nd to increased erythropoiesis
- anaphylaxis
- Hyperkalaemia in uraemic patients
- ↑mortality of patients with malignancy (e.g. renal cell carcinoma)

Causes of response failure to erythropoietin therapy:

- · iron deficiency
- · inadequate dose
- concurrent infection/inflammation
- hyperparathyroid bone disease
- aluminium toxicity: if suspected, perform a desferrioxamine test
- folate deficiency

- marrow fibrosis
- development of antibodies against the treatment
- ESA-induced PRCA
- testosterone deficiency in males
- · poor compliance

ESA induced pure red cell aplasia (PRCA)

- due to antibodies against erythropoietin
- Indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies.
- Confirmed by presence of anti-erythropoietin antibodies together with a lack of pro erythroid progenitor cells in the bone marrow
- the risk is greatly reduced with darbepoetin

Treatment protocol

- Ideally, before starting EPO in renal patients you should get their haematinics (iron, B12, folate) to ensure they are replete of all. If any are found to be low they should be replaced.
- Parameters commonly measured to assess iron status are: serum ferritin and transferrin saturation.
 - ➤ Both are <u>indirect measures of iron</u> and frequently do not permit an assessment of the adequacy of iron supply to the erythron.
 - direct measures by flow cytometry, cell volume and hemoglobin concentration can be measured in individual red blood cells and reticulocytes, using two parameters (particularly useful in identifying iron-deficient erythropoiesis).
 - The percentage of hypochromic erythrocytes (defined as red blood cells with a hemoglobin concentration of less than 28 g/dl)
 - the content of hemoglobin in reticulocytes (CHr)
- If there is Iron deficiency (NICE 2015)
 - ➤ For patient on haemodialysis or ESA → I.V iron therapy.
 - ➤ For patient not on haemodialysis → trial of oral iron
 - ➤ If they are intolerant of oral iron or target Hb levels are not reached within 3 months → intravenous iron therapy. (part 2 Exam July 2002)
 - ➤ offer maintenance iron to people with anaemia of CKD who are receiving ESAs
 - haemodialysis patients will need the equivalent of 50–60 mg intravenous iron per week (1 mg/kg/week). [NICE 2015]
- If Ferritin is below the recommended level of 200 for patients receiving erythropoietin treatment → iron supplementation is recommended.
 - GI absorption of iron is suboptimal in patients with renal failure, and IV replacement is therefore the preferred intervention.
- Erythropoietin is given subcutaneously at a dose of 25-50 U/kg three times per week
- The blood pressure, haemoglobin and reticulocyte count should be monitored every 2 weeks
- erythropoiesis-stimulating agent (ESAs): dose and frequency
 - > adjusted to keep the rate of Hb increase between 10 and 20 g/litre/month.
- Adjusting ESA treatment
 - if ACEi & ARB are used, an increase in ESA therapy should be considered.

ferritin should be >200g/l in patients treated with EPO.

Significance of erythropoietin levels (EPO test)

- Low serum erythropoietin levels suggest → polycythaemia vera
- raised serum erythropoietin level suggests→
 - hypoxic cause
 - > autonomous production of erythropoietin (as in renal carcinoma).
 - > erythropoietin abuse (Erythropoietin has been misused as a performanceenhancing drug by some athletes)

May 2010 exam: H/O CKD patient started on erythropoietin. What is the main benefit of this treatment?

→ Improved exercise tolerance

Erythropoietin can be detected in urine for few weeks after the latest dose

Renal replacement therapy

CKD on haemodialysis - most likely cause of death is IHD

Patients usually begin dialysis when their glomerular filtration rate (GFR) reaches 10 ml/minute or 15 mL/minute if they are diabetic.

Indications for dialysis

- · Refractory pulmonary oedema
- Persistent hyperkalaemia (K+ >7mmol/L)
- Severe metabolic acidosis (pH<7.2 or base excess <10)
- Uraemic complications such as
 - encephalopathy or
 - Uraemic pericarditis (pericardial rub)
 - Uraemic peripheral neuropathy
- Drug overdose—BLAST: Barbituates, Lithium, Alcohol (and ethylene glycol), Salicylates, Theophyline.

Vascular access for routine haemodialysis

- Arterio-venous fistula:
 - Current Renal Association guidelines state that an arterio-venous fistula is the first choice of vascular access for dialysis.
 - arterio-venous fistulas are preferred due to their longevity and lower risk of infection.
 - > Arterio-venous grafts:
 - using prosthetic material,
 - have a reduced longevity compared to arterio-venous fistulas.
 - These are second choice preference for vascular access.
 - Dialysis catheters (tunnelled and non-tunnelled):
 - carry a risk of infection and are not preferred as first line.
 - They can be used when emergency dialysis is required, or as an interim measure when awaiting more permanent dialysis access.

Arterio-venous fistula is the first choice of vascular access for dialysis.

Haemodialysis (HD)

Assessment of haemodialysis adequacy:

The adequacy of haemodialysis session is best measured by :

- 'Clearance' is used to indicate dialysis adequacy, and most commonly the clearance of urea is used.
 - Clearance is the ratio of removal rate to blood concentration.
 - Removal rate can be measured by sampling blood on either side of the dialyser and multiplying the difference by the inflow rate.
 - Clearance is the removal rate divided by the inflow concentration.
 - However, this only provides a measure of dialysis at one point in time.
- The adequacy of an **entire haemodialysis session** is best measured by the fall in solute concentration from before dialysis to after.
 - This is calculated using complex equations and is expressed as Kt/V.
 - The current recommendation for adequate dialysis for three treatments per week are a Kt/V of 1.2.
- (the 'urea reduction ratio'). A more crude assessment of the adequacy of dialysis obtained by noting the magnitude of the decrease in blood urea concentration
- It is standard practice in the UK to take biochemical and haematological measurements before and after haemodialysis sessions at regular intervals (monthly in hospital HD patients and at least 3 monthly in home HD patients). Adequate HD is indicated by:
 - pre-dialysis serum bicarbonate levels of 18-24 mmol/L,
 - > potassium 4.0-6.0 mmol/L,
 - > phosphate 1.1-1.7 mmol/L,
 - calcium and albumin within normal range.

Pre and post- dialysis values:

- A high pre-dialysis or inter-dialysis blood pressure may be related to:
 - excessive sodium and water ingestion during the inter-dialysis period
 - > or a high dialysate sodium level.
- A high post-dialysis blood pressure may reflect inadequate achievement of dry weight.
 - Volume and blood pressure are linked and it is therefore important to optimise ultrafiltration and dry weight to control blood pressure.
 - A patient's dry weight is their normal weight when they are not fluid overloaded, also called euvolemia
 - The rate of ultrafiltration depends upon the porosity of the membrane and the hydrostatic pressure of the blood, which depends upon blood flow. This is very effective in removal of fluid and middle-sized molecules, which are thought to cause uremia.
- Weight gain between dialyses of more than 4.8% is associated with increased mortality.
- The combination of high pre- and post-dialysis blood pressure, and high pre-dialysis potassium, indicate that the patient is receiving inadequate dialysis.
 - Both procedural issues (insufficient blood flow rate, dialysis time and frequency and needle size) and access issues should be addressed.

- If these fail to improve the situation a different dialysis modality should be considered, such as more frequent or sustained haemodialysis.
- It is recommended that pre-dialysis haemoglobin concentration should be maintained between 100-120 g/L.
 - If his haemoglobin below the recommended level for a dialysis patient, you need to measure haematinics initially prior rather than jumping in with EPO treatment.
 - Many haemodialysis patients are iron deplete, and in these cases intravenous iron is indicated rather than EPO in the first instance.

Adverse effects of dialysis

- Modem techniques of dialysis preclude chances of vitamin D or calcium deficiency, fluid and electrolyte imbalance or risk of viral hepatitis
- protein-calorie malnutrition is the most common problem associated with haemodialysis
 - > seen in up to 50% of patients
 - Dietary restriction of foods with high phosphate content (milk, eggs and cheese), decreased protein intake, anorexia, nausea and vomiting, may all contribute to this condition

Complications of rapid haemodialysis

- Disequilibrium syndrome:
 - Caused by cerebral oedema, resulting from the rapid shifts of uraemic toxins associated with too-rapid haemodialysis in a severely uraemic patient
 - characterized by weakness, dizziness, headache, and in severe cases, mental status changes.
 - > The diagnosis is one of exclusion:
 - > a prime characteristic of this syndrome is that it is nonfocal.

Long-term haemodialysis

- associated with carpal tunnel syndrome this is due to beta-2 microglobulin deposition
- Cardio-vascular disease is the commonest cause of death (50%) in dialysis patients
- Carnitine deficiency
 - > Patients on chronic hemodialysis may have carnitine deficiency.
 - Carnitine is essential for the transport of long-chain fatty acids from the cytosol into the mitochondria.
 - ➤ chronic hemodialysis → carnitine deficiency → Impaired mitochondrial transport of long-chain fatty acids
 - Cardiomyocytes and skeletal muscle cells extensively use fatty acids as a fuel.
 - > Carnitine deficiency leads to:
 - accumulation of long-chain fatty acids in the cytosol of cardiomyocytes (resulting in cardiac fatty change and cardiomegaly)
 - accumulation of long-chain fatty acids in the cytosol of skeletal muscle cells (resulting in muscle cramps).
 - > Treatment is via L-carnitine administration.

Line-related infection

A patient with a tunnelled haemodialysis catheter who develops a fever on dialysis should be considered to have line-related infection until proven otherwise.

- The most common organisms for line-related sepsis are gram-positive bacteria, namely *S. aureus*.
- Blood cultures should be taken from the line and peripherally, and if the same organism is growing from them both, this strongly suggests the line is the source of the infection.
- Indications of Catheter removal :
 - Staphylococcus aureus bloodstream infection
 - non-staphylococcus aureus catheter-related bloodstream infection in the following circumstances:
 - Severe sepsis
 - Haemodynamic instability
 - Endocarditis
 - Evidence of metastatic infection, or
 - Persistence of bacteraemia after 48-72 hours of effective antibiotics.
- Treatment
 - Methicillin-resistant Staphylococcus aureus (MRSA) infection
 - vancomycin is the drug of choice

Dialysis amyloidosis

Aetio-pathogenesis

- Occurs due to the failure of clearance of B2-microglobulin
 - This protein, the light chain of class-1 HLA antigens, is usually freely filtered at the glomerulus but is not cleared by cellulose-based dialysis membranes
- There is resulting amyloid deposition within the synovium

Clinical features: Amyloid deposition within the synovium results in:

- clinical syndrome of median nerve compression
- pain and stiffness in multiple joints

Treatment & Prognosis

- The syndrome resolves slowly after renal transplantation,
- some benefit is seen in switching patients to dialysis with a biosynthetic dialysis membrane

Complications:

 gastrointestinal haemorrhage caused by amyloid deposition around submucosal blood vessels

Peritoneal dialysis

- Peritoneal dialysis (PD) is a form of renal replacement therapy. It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week.
- The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day.

Complications:

- · Peritoneal dialysis-associated peritonitis
- sclerosing peritonitis
- Adynamic bone disease (ABD)

Peritoneal dialysis-associated peritonitis

- Causes:
 - ➤ The most common cause → coagulase-negative staphylococci such as Staphylococcus epidermidis (40-50% of cases).
 - ➤ another common cause → Staphylococcus aureus
- Diagnosis
 - is made by peritoneal fluid cell count (neutrophils above 100/ml).(White cell count > 100/mm³ in PD fluid sample)
 - > PD fluid neutrophil percentage of greater than 50% is in keeping with PD peritonitis.
- Treatment
 - intraperitoneal antibiotics (vancomycin) And oral quinolone (Before culture results are received).
 - the initial treatment of choice would be intraperitoneal antibiotics.
 - initial antibiotic regimes should cover Gram positive (including MRSA) and Gram-negative organisms.
 - Give intra-peritoneal vancomycin and gentamicin
 - Intravenous antibiotics would be preferable if the clinical condition worsened despite intraperitoneal antibiotics,
 - Recurrent Staph, epidermidis peritonitis may necessitate removal and replacement of the peritoneal dialysis catheter due to chronic colonisation

Adynamic bone disease (ABD) → (low bone turnover)

- Definition: (ABD) is a variety of renal osteodystrophy characterized by reduced osteblasts and osteoclasts, no accumulation of osteoid and markedly low bone turnover (↓bone formation and resorption).
- Distinguish ABD from the second low-turnover form, i.e. osteomalacia:
 - In ABD: Both the rate of collagen synthesis by osteoblasts and the subsequent mineralization of bone collagen are subnormal, there are few or no osteoblasts
 - In osteomalacia: mineralization defect exceeds the defects in bone formation, resulting in a relative osteoid excess.
 - > Bone alkaline phosphatase (BAP) is the single most useful biochemical parameter for the assessment of bone formation.
 - ↑↑ BAP exclude ABD
 - elevations of BAP along with total AP may be seen in severe osteomalacia.
- Risk factors & Causes: overtreatment of secondary hyperparathyroidism associated with CKD (ABD is, at least in part, often iatrogenic)
 - > commonly CKD patients on dialysis, either peritoneal or hemodialysis
 - ↑ in CAPD compared to haemodialysis
 - Especially prevalent in diabetic patients on peritoneal dialysis
 - ↑ in age of dialysis patients
 - Aluminum overload
 - Serum aluminium levels do not correctly reflect body aluminium stores and do not correlate well with signs of aluminium toxicity.
 - desferrioxamine (DFO) test increases the diagnostic accuracy
 - > High calcium load
 - Low PTH levels
 - Vitamin D over-treatment (eg : alfacalcidol)
 - High prevalence of diabetes mellitus
- Pathophysiology:
 - basically in CKD:
 - PTH serum levels are higher than normal

- bone tissue is resistant to PTH
- > PTH serum levels decrease beyond relatively low levels, which would be considered normal in the general population.
- ➤ So that a relative reduction of PTH → low turnover state.
- Complications: (pain, fracture,↑ Ca+)
 - bone pain
 - increased incidence of hip fracture
 - > hypercalcaemia as the bone loses its capacity to buffer serum calcium
- Treatment: currently follows two principles:
 - 1. reduce calcium and vitamin D load
 - Stop calcium-containing phosphate binders and replace with non-calcium-non-aluminium-containing phosphate binders
 - Assess oral dietary calcium intake and reduce to <2000 mg/day
 - Reduce or stop active vitamin D compounds
 - Lower dialysate calcium to 1.25 mmol/L or below
 - Avoid bisphosphonates, strontium and fluoride administration
 - 2. restore PTH activity
- Follow- up
 - Changes of bone markers, such as bone-specific alkaline phosphatase, over time, may be suitable indicators for the assessment of therapeutic effects.

Other complications of peritoneal dialysis

- . Worsening of diabetic control:
 - > dialysis fluid contains a high glucose
 - patients with diabetes may require significantly more diabetes treatment to reduce their blood glucose once dialysis is commenced
- Worsening of abdominal hernias: due to the large fluid volume expansion and should be surgically repaired
- Stomas adhesions:
 - > Stomas may be associated with significant adhesions and changes within the abdominal cavity making catheter placement impossible

Contraindication of continuous ambulatory peritoneal dialysis (CAPD):

- · Colostomy.
 - increase the risk of peritonitis
- Recent or prospective abdominal surgery
 - Complex abdominal surgery and resultant extensive adhesion damage the peritoneal membrane (peritoneal fibrosis) and lead to compartments within the peritoneum.
 - Simple abdominal surgery, however, does not preclude peritoneal dialysis; examples include cholecystectomy, appendectomy or caesarian section.

May 2013 exam: A patient on Ambulatory Peritoneal Dialysis (CAPD). Feels generally unwell with abdominal pain and fever. Which organism is most likely to be responsible for this presentation?

→ Staphylococcus epidermidis

Renal transplant

Cytomegalovirus is the most common and important viral infection in solid organ transplant recipients

Hyperacute graft rejection is due to preexistent antibodies to HLA antigens and is therefore IgG mediated

Renal transplant HLA matching → DR is the most important

Some basic points on the HLA system

- · class 1 antigens include A, B and C. Class 2 antigens include DP, DQ and DR
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows DR > B > A
- Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection?
 - > HLA-C
 - Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection;
 - specifically, HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant.

Types of Transplants:

- Autografts:
 - > same individual acts as both donor and recipient.
- Isografts:
 - > donor and recipient are genetically identical (twins).
- Allografts:
 - donor and recipient are genetically dissimilar but belong to the same species (the commonest).
- · Xenografts:
 - donor and recipient belong to different species (between animal and human).
- Orthotopic transplants:
 - the transplanted part is placed in its normal anatomical location.
- Heterotopic transplants:
 - the transplanted part is placed in different anatomical location.

Graft survival	1 year	10 years
Cadaveric transplants	90%	60%
Living-donor transplants	95%	70%

Post-operative problems

- ATN of graft
- · vascular thrombosis
- · urine leakage
- UTI

Hyper acute rejection (minutes to hours)

- due to pre-existent antibodies against donor HLA type 1 antigens (a type II hypersensitivity reaction) and is therefore IgG mediated
- · rarely seen due to HLA matching
- antigen-antibody complexes → activate the complement system → causing massive thrombosis in the capillaries → avascularization of the graft.

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 the kidney is most susceptible to hyperacute rejection; the liver is relatively resistant, possibly because of its dual blood supply, but more likely because of incompletely understood immunologic properties.

Reasons for deterioration in renal function soon after a renal transplant:

- Hyperacute rejection (which usually occurs in hours)
- · Acute tubular necrosis, and
- Surgical complications (renal arterial or venous thrombosis and ureteric stenosis).

In the presence of a dropping urine output and rising creatinine, an <u>urgent ultrasound scan</u> should be obtained <u>to exclude any mechanical obstruction of the renal tract</u> before considering other options.

Acute graft failure (< 6 months)

- Approximately 25% of transplant patients will have at least one episode of rejection mostly between days 7 and 21, and less commonly up to three months post-operation.
- usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- other causes include cytomegalovirus infection
 - Although CMV infection would not cause a <u>sudden</u> deterioration in renal function
- Doppler ultrasound studies may show a sharp deterioration in graft perfusion, and kidney biopsy will show invading lymphocytes penetrating the tubular basement membrane, causing tubulitis.
- It is often clinically silent, with only a sharp rise in serum creatinine pointing towards the diagnosis.
- may be reversible with steroids and immunosuppressants

Chronic graft failure (> 6 months)

- both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy)
- caused by recurrence of original renal disease (MCGN > IgA > FSGS)
 - ⇒ Recurrence of renal pathologies post-renal transplantation:
 - 1. Membranoproliferative GN: 40-90% recurrence rate, type 2 much greater than type 1).
 - 2. FSGS: 40%.
 - 3. Membranous GN: 30%.

Differentiate between acute cellular rejection and CMV

	Onset	Feature	Renal function
Acute cellular	Commonly between	often clinically silent	Sudden sharp rise
rejection	days 7 and 21		in serum creatinine
CMV	Usually seen after	Systemic feature (pulmonary,	Gradual rise in
	four weeks	GIT and Retinitis).	serum creatinine

Risk factors of chronic rejection include:

- number of previous acute rejection episodes
- presence of anti-HLA antibodies
- · anti-endothelial antibodies
- CMV infection
- dyslipidaemia
- hypertension
- functional mass of the donor kidney, and
- delayed graft function (a clinical manifestation of ischaemia/reperfusion injury).

Type of transplant rejection	Hyperacute rejection	Acute rejection	Chronic rejection
Frequency	• < 1%	• 50%	• 50%
Onset after transplantation	• <48 (usually within minutes to hours)	< 6 months (usually within days to weeks)	> 6 months (usually after a few years)
Pathophysiology	Preformed antibodies against class I HLA → activation of complement system and adhesion to granulocytes → thrombosis of vessels → graft ischemia	T-lymphocyte induced cell- mediated and/or humoral immunity	Irreversible intimal fibrosis and obstruction of vessels
Clinical findings	Intraoperative assessment: swelling of the organ as soon as perfusion is restored	 Pain in the graft region Graft edema Fever and deterioration of general condition In kidney transplants: ↑ BP and RFT; ↓urine output 	Slow, progressive loss of organ function
Diagnosis	Biopsy: small vessel thrombosis and graft infarction	Biopsy (confirmatory test) Heterogenous mononuclear aggregates± antibody deposition C4d staining indicates humoral graft rejection Negative C4d staining indicates cellular rejection	Biopsy Kidney: Glomerular sclerosis Heart: accelerated coronary artery disease Liver: vanishing bile duct syndrome
Prevention	Preoperative cross- matching, ABO grouping and HLA matching	Post-transplant immunosuppressive therapy	Irreversible process with no known prevention
Treatment	Graft removal	Change or increase dosage of immunosuppressive therapy	Graft removal, and re-transplantation

<u>Graft versus host disease (GVHD)</u>

presents with liver abnormalities, significant diarrhoea and skin changes.

Definition

 damage to the host as a result of a systemic inflammatory reaction induced by T lymphocytes present in the graft

Etiology

- Allogenous hematopoietic stem-cell transplantation
- Small bowel transplantation
- Transfusion of non-irradiated blood products
 - > Products implicated in cases of transfusion associated GVHD include:
 - Non-irradiated whole blood
 - Packed red blood cells
 - Platelets
 - Fresh non-frozen plasma
 - Granulocytes
 - > The following have not been implicated:
 - Frozen deglycerolised red blood cells
 - FFP and
 - Cryoprecipitate

Types of graft-versus-host disease

	Acute graft-versus-host disease	Chronic graft-versus-host disease
Onset	< 100 days after transplantation	> 100 days after transplantation
Pathophysiology	Donor T lymphocytes react with the recipient's organs	Mostly unknown
Clinical presentation	 Pruritic or painful maculopapular rash Nausea, vomiting, diarrhea, and/or cramping abdominal pain Hepatic dysfunction: jaundice 	Scleroderma-like and lichenoid skin changes Sicca syndrome: xerophthalmia, xerostomia, dry pruritic skin Chronic enteritis (similar to inflammatory bowel disease): bloody diarrhea, abdominal pain, weight loss Hepatic dysfunction: jaundice Bronchiolitis obliterans: chronic cough, wheezing, and dyspnea that is not responsive to bronchodilator therapy Myasthenic symptoms polymyositis: weakness, muscle pain
Diagnostics	CBC: anemia, thrombocytopenia, leukope nia ↑ ALP Confirmatory test: biopsy of skin, rectum, or liver	 Spirometry: obstructive lung disease Confirmatory test: biopsy of the skin, oral cavity, liver, or lung
Prevention	 Antithymocyte globulin Cyclosporine and one of the following: Methotrexate Mycophenolate mofetil 	
Treatment	Optimize GvHD prophylaxis (e.g., cyclosporine levels) Corticosteroids < 50% skin involvement: topical steroids Involvement of the GI tract, liver, or > 50% of skin: systemic steroids ± topical steroids	 First-line: corticosteroids Second-line: cyclosporine and increased corticosteroid dose

Post-transplant problems

Cytomegalovirus (CMV) infection

Renal transplant + infection → CMV

Epidemiology

Over 50% of renal transplant patients have a significant infection within the first 12 months of having a renal transplant.

Risk factors

- Two main factors determine whether a patient will develop CMV infection after transplantation:
 - Whether the donor or recipient harbours a latent virus capable of reactivation after transplantation
 - At the time of transplant, the CMV-serological status of the donor and recipient are noted.
 - the highest risk is seen in CMV-seronegative recipients who receive a kidney from a CMV-seropositive donor.
 - These patients are usually given antiviral prophylaxis.
 - Primary disease is the commonest and most severe type of posttransplant CMV infection.
 - This occurs in individuals who have never been infected with CMV who receive an allograft that contains latent virus from a CMV-seropositive donor.
 - The degree of immunosuppression after transplantation.
 - CMV infection occur as a result of immunosuppression
 - Usually seen after four weeks as before this time the immune system has not been fully affected by the immunosuppressants.

Features

- ⇒ Interstitial pneumonitis
- ⇒ Oesophagitis
- ⇒ Peptic ulceration
- ⇒ Retinitis.

Complications

- graft rejection
- renal artery stenosis.

Management

- ⇒ Ganciclovir (synthetic guanine derivative) is the most appropriate treatment for CMV
 - concomitant use with ciclosporin leads to elevated creatinine
 - Pancytopenia may occur as a result of ganciclovir toxicity
- ⇒ Foscarnet is the drug of choice for ganciclovir-resistant cytomegalovirus retinitis.

the two most common causes of declining renal function post renal transplant are:

- graft rejection and
- ciclosporin toxicity.

Acute pyelonephritis:

 high risk of acute episode of pyelonephritis in the transplanted kidney, due to the immunosuppression, the neuropathic bladder and self-catheterisation.

- present like an acute rejection episode, with a tender swollen graft, low-grade pyrexia, and deteriorating graft function.
- Especially in the intermediate stage of the post-transplantation immunosuppression, when the patient is most immunocompromised (three to six months post-transplant).

Interstitial pneumonia

- Cytomegalovirus is the predominant cause of infection in patients within a period of 1-4 months after renal transplantation
- A chest X-ray will show a bilateral interstitial or reticulonodular infiltrate that begins in the periphery of the lower lobes and spreads centrally and peripherally

BK virus:

• C4d staining is used for detection of BK virus after renal transplantation

Epstein-Barr virus (EBV)

- Epstein-Barr virus (EBV)-associated lymphoproliferative disease (e.g: non-Hodgkin's lymphoma) may occur in individuals with inherited or acquired immunodeficiency syndromes.
- Approximately 1% of renal transplant recipients develop post-transplant lymphoproliferative disease (PTLD) in the first year following their transplant.

skin cancer

- Kidney transplant recipients have a high risk of developing non-melanoma skin cancer, therefore, cancer surveillance is an important consideration in kidney transplant recipients.
- The patient may has a malignant melanoma with liver metastases, hence the deranged liver function tests and liver capsule pain.
- The patient is often unaware of the melanoma lesion, and the primary lesion may in fact disappear as the disease progresses. Patient may present with RUQ pain and high LFT.
- Post-transplant patients are much more prone to develop malignancy compared to normal population.
 - ⇒ Cyclosporine is one of the main reasons for development of post-transplant malignancy.
- Non-melanoma skin cancers (NMSC) are the commonest malignancies in post-transplant state. Of these, squamous cell Ca is the commonest.

Kidney donation

- Providing there is a sibling who is proven not to have polycystic kidney disease, living
 related donation should be considered as this would ensure a better match and better graft
 survival
- Siblings are close genetically, and therefore usually are a better match than spouses. The husband should not be accepted for kidney donation until all siblings have been considered
- The age difference is not, however, a contraindication to kidney donation.
- Living unrelated kidney donation could also be considered, and is increasing in use in the UK
- Adults should be considered as doner prior to children because renal cysts usually develop during teenage years, so one cannot be confident a child has not been affected until they are at least 20.

Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD type 1 = chromosome 16 = 85% of cases

ADPKD type 2 = chromosome 4 = 15% of cases

Ultrasound is the screening test for adult polycystic kidney disease

Epidemiology

- · ADPKD is the most common inherited cause of kidney disease,
- affecting 1 in 1,000 Caucasians.
- Accounting for approximately 8% of cases of end-stage renal disease (ESRD).
- Typically presents between the ages of 30-50.

Genetics

- Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively
- As it is an autosomal dominant, the chance of passing this condition from affected patient to his son is 50%.

Types

ADPKD type 1	ADPKD type 2
85% of cases	15% of cases
Chromosome 16	Chromosome 4
Presents with renal failure earlier, reach ESRF by	Have a slower course, reaching ESRF by
50s.	70s.

Features

- Hypertension (the **earliest** manifestation of ADPKD)
- recurrent UTIs
- abdominal pain (loin pain due to a cyst haemorrhage or infection)
- renal stones
- haematuria (rupture cysts presents with visible haematuria) (Gross haematuria in ADPKD carries a poor prognosis however microscopic haematuria may be a complication)
- · chronic kidney disease

Renal Complications

- CKD
 - ⇒ ADPKD is like a CKD with high phosphate, low calcium but with normal/high Hb due to excess erythropoietin secretion.
- Excessive erythropoietin production → polycythaemia.
- Renal cell carcinoma with lung metastasis: it is very rare but recognized complication of ADPCKD → CT Thorax & Abdomen.

Extra-renal manifestations

- Liver cvsts (70%)
- Berry aneurysms (8%)

- ⇒ Subarachnoid haemorrhage may be a cause of mortality in 9% of patients with ADPKD.
- ⇒ 8% of patients have an asymptomatic intracranial aneurysm
- ⇒ screening for cerebral aneurysms should only be carried out in high risk patients. These include factors such as:
 - 1. Previous rupture of aneurysm
 - 2. Concerning neurological symptoms (for example, severe headache)
 - 3. Positive family history of haemorrhagic stroke or aneurysm.
- ⇒ Even if aneurysms are found, the rupture risk can still be low, and the morbidity implications of curative surgery may outweigh conservative management.
- Cardiovascular system: mitral valve prolapse (25%) → (needs echo screening), mitral/tricuspid incompetence, aortic root dilation, aortic dissection
- Colonic diverticula (with any related symptoms, screen by barium enema)
- cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary **Investigations**
 - **Ultrasound** (Sensitivity for ADPKD1 is 99% for at-risk patients older than 20 years)
 - ⇒ Sonographic diagnostic criteria (in patients with positive family history):
 - age < 30 years → 2 unilateral or bilateral cysts
 - age 30-59 years → 2 cysts in each kidney
 - age > 60 years → 4 cysts in each kidney
 - ⇒ Sensitivity of these criteria
 - nearly 100% for patients 30 years of age or older and for younger patients with PKD1 mutations.
 - 67% for patients with PKD2 mutations younger than 30 years of age.
 - CT scan or MRI should therefore be used in the latter group.
 - one cannot be confident a child has not been affected until they are at least
 20:
 - a normal ultrasound scan at 20 years of age means you can be 90% confident they are not affected,
 - ❖ a normal scan at 30 increases the confidence level to 98%.
 - ⇒ Screening is not usually recommended in children because the presence or absence of cysts does not affect management (tight blood pressure control), and the absence of cysts in children does not exclude the disease.
 - ⇒ All children of affected patients should have their blood pressure monitored at least annually, from early childhood (around age 3) onwards.
 - ⇒ If cysts are not seen in a younger with a positive family history, the ultrasound should be repeated every five years until the age of 30.

Contrast-enhanced CT scan or MRI

- ⇒ Abdominal CT is sensitive for the detection of cysts however the high radiation dose, particularly in young patients, means it is not widely used as a screening test.
- ⇒ should be used if ultrasound is equivocal, especially in patients with PKD2 mutations younger than 30 years of age.
- ⇒ **CT**: More sensitive than USS and may aid in diagnosis in younger patients.
- ⇒ *MR angiography*: In patients with a family history of intracranial aneurysm to screen for cerebral aneurysms.

Genetic testing

The most appropriate strategy to investigate younger with a family history of ADPK is genetic counselling (referral)

- ⇒ The major indication for genetic screening in (ADPKD) is <u>for subjects who are</u> considering donating a kidney to a relative affected by the disease
- ⇒ **sequence analysis** can identify only around 70% of known mutations and **linkage analysis** requires the availability of sufficient family members.
- ⇒ can be used in the following cases:
 - The imaging results are equivocal or inconclusive.
 - To confirm a presumed diagnosis in the absence of family history of the disease (conclusive proof of the diagnosis in these patients relies on mutation analysis).
 - When a definite diagnosis is required in a younger patient, such as a potential living related kidney donor.
- Renal biopsy is contraindicated due to a high risk of haemorrhage into a cyst

Treatment

- high fluid intake (to prevent the formation of renal stones or blood clots)
- non-NSAID-based analgesia are the cornerstones of management
 - ⇒ IV fluids, paracetamol and codeine
- Hypertension → ACE inhibitors or angiotensin receptor antagonists
 - ⇒ ACE inhibitors reduce proteinuria and may reduce cyst formation in ADPKD,
 - ⇒ aliskiren, the direct renin inhibitor, also has early data which show promise with respect to reducing new cysts.
- A new therapy (tolvaptan) to delay disease progression (recommended by NICE in 2015)
 - ⇒ Action: selective vasopressin antagonist → inhibit the binding of vasopressin to the V2 receptors → reduces cell proliferation, cyst formation and fluid excretion.
 - ⇒ **adverse reactions:** thirst, polyuria, nocturia, pollakiuria (frequent urination),↑ liver enzyme.
- Urinary tract infections should be treated with lipophillic drugs (for example, ciprofloxacin, trimethoprim-sulphamethoxazole) as they have the best penetration into cyst fluid.
- The patient should be offered **genetic counselling**, despite the fact that the disease has a variable clinical course even between affected family members.
- End-stage renal disease → Transplantation

Prognosis

- the renal function usually deteriorates in a gradual fashion, usually with a drop in creatinine clearance of 5/6 ml/min/year
- Approximately half of patients require dialysis by the age of 60

MRCPUK-part-1-January 2016 exam: You are reviewing a patient with adult polycystic kidney disease. Which cardiovascular feature are you most likely to find on examination?

→ Mitral valve prolapse

Autosomal recessive polycystic kidney disease (ARPKD)

- Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD).
- It is due to a defect in a gene located on chromosome 6
- Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure. Newborns may also have features consistent with Potter's syndrome secondary to oligohydramnios.
- End-stage renal failure develops in childhood.
- Patients also typically have liver involvement, for example portal and interlobular fibrosis.
- Renal biopsy typically shows multiple cylindrical lesions at right angles to the cortical surface.

Medullary sponge kidney

- is a disorder characterised by <u>dilatation of the collecting ducts in the papillae</u>, with accompanying cystic changes
- It is often associated with **calculi**, which can result in pyelonephritis and renal tract obstruction.
- Typically, not inherited but is a congenital condition. The aetiology is uncertain, but it is thought to be a developmental abnormality, possibly resulting from tubular or collecting duct obstruction at any early age.
- The kidneys size are normal or increased.
- The age of presentation is usually in the third or fourth decade
- The majority of cases are sporadic, although a rare autosomal dominant familial form exists
 with onset in adulthood, and a juvenile autosomal recessive form is also recognised.
 Recent research has identified a possible defect in the development of the proton pump
 mechanism in the kidney.
- Diagnosis
 - Diagnosis is made via excretion urography, showing small calculi in the papillary zones with surrounding increase density; this is because the dilated collecting ducts are filled with contrast medium
 - > About 20% of patients have associated hypercalciuria or renal tubular acidosis
 - Skeletal hemihypertrophy may be associated
 - Renal failure is highly unusual

Alport's syndrome

Alport's syndrome - X-linked dominant (in the majority)

Alport's syndrome - type IV collagen defect

- Alport syndrome is the second most common inherited cause of renal failure (after polycystic kidney disease)
- usually inherited in an X-linked dominant pattern.
 - ➤ Inheritance is variable, but the majority are X linked dominant (85%);
 - Therefore, as only the Y chromosome is passed from father to son there is no chance of the son having the disease.

- > 15% are autosomal recessive with rare autosomal dominant variants
- Most cases arise from the COL4A5 gene on the X chromosome .
- It is due to a defect in the gene which codes for type IV collagen resulting in an abnormal glomerular-basement membrane (GBM).
 - Patients with Alport syndrome are at risk of developing antiglomerular basement membrane disease (Goodpasture's disease) following transplantation, as their immune systems have never been exposed to type IV collagen and hence lack tolerance.
 - What is the most likely reason for the decline in graft function?
 - Anti-glomerular-basement membrane antibodies (Goodpasture's syndrome)
- There is a high spontaneous mutation rate, which means 20% of patients have no family history.
- Prevalence is around 1 in 5000
- The disease is more severe in males with females rarely developing renal failure
- usually presents in childhood.
- more severe in males
 - > females do not develop progressive renal failure with this condition.
- A favourite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies leading to a Goodpasture's syndrome like picture

Features

"Can't see, can't pee, can't hear a bee."

- microscopic haematuria
 - Most common and earliest manifestation
- progressive renal failure
- bilateral sensorineural deafness (usually occurs before the onset of renal failure)
- ocular
 - > Anterior lenticonus
 - protrusion of the lens surface into the anterior chamber
 - Occurs in 25% of patients
 - is the **pathognomonic** feature of Alport syndrome
 - Dot-and-fleck retinopathy
 - Most common ocular manifestation of patients with Alport syndrome, (occurring in 85%)
 - > retinitis pigmentosa

Investigations

- · renal biopsy:
 - Light microscopy
 - usually unremarkable and electron microscopy is usually required.
 - > Electron microscopy
 - splitting of lamina densa
 - basket weave pattern of glomerular basement membrane
 - foam cells
 - produced by lipid accumulation in visceral epithelial cells
- slit lamp examination:
 - bilateral thin lens capsules
 - conical protrusions on the anterior aspect of the lens.
 - > subcapsular cataracts.

Treatment

- Rigorous control of hypertension may delay the onset of end stage renal failure.
- angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers if they have proteinuria
- Renal transplant

Prognosis

• ESRF seen in 90% of patients with Alport's by the age of 40 years.

MRCPUK-part-1-September 2009 exam: What is the mode of inheritance of Alport's syndrome in the majority of cases?

→ X-linked dominant

MRCPUK-part-1-January 2008 exam: Alport's syndrome is due to a defect in:?

→ Type IV collagen

Haemolytic uraemic syndrome

The presence of **thrombocytopenia** and evidence of **haemolysis** in association with **bloody diarrhoea** should make you think of haemolytic uraemic syndrome (HUS).

Haemolytic uraemic syndrome - classically caused by E coli 0157:H7

Haemolytic uraemic syndrome is generally seen in young children and produces a triad of:

- · acute renal failure
- microangiopathic haemolytic anaemia
- thrombocytopenia with normal clotting.

Causes

- post-dysentery classically E coli 0157:H7 ('verotoxigenic', 'enterohaemorrhagic')
 .Toxins produced in the intestine enter the blood and bind to endothelial cells in target organs. Endothelial cell damage leads to platelet and fibrin deposition with resultant fragmentation of circulating red blood cells and microvascular occlusion.

 The syndrome has also been reported after infections with coxsackie, echovirus and Shigella.
- tumours
- pregnancy
- · ciclosporin, the Pill
- · systemic lupus erythematosus
- HIV
- Inherited recurrent HUS has been described with both dominant and recessive patterns of inheritance

Investigations

- full blood count: anaemia, ↓↓Serum haptoglobins (which bind haemoglobin), thrombocytopaenia, fragmented blood film
 - ➤ The hallmark of HUS is the appearance of schistocytes (fragmented, deformed, irregular, or helmet shaped red cells) on the blood film.
- There is normal coagulation and fibrinogen.
- U&E: acute renal failure
- · stool culture

Major differential diagnosis is:

- 1. Sepsis with DIC presents with abnormalities of clotting parameters.
- 2. TTP thrombotic thrombocytopenic purpura presents with microangiopathic haemolytic anaemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease.
 - ➤ Patients with TTP lack a plasma protease that is responsible for the breakdown of von Willebrand factor (vWF) multimers and these accumulate in the plasma. The activity of this protease is normal in patients with HUS.
 - Until the test for vWF protease activity becomes available, differentiation between HUS and TTP is based on the presence of central nervous system involvement in TTP and the more severe renal involvement in HUS.
 - ➤ In HUS 90% of patients are children and a history of prodromal diarrhoeal illness is more common.

feature	HUS	TTP
Acute kidney injury	more severe	Less severe
Neurological symptoms	less common	More common

Complications include:

- Stroke, seizure and coma occur in 25% of patients
- · Rarely pancreatitis, and
- · Pleural and pericardial effusions.
- Approximately 5% of patients will develop end stage renal failure.

Management

- treatment is supportive e.g. Fluids, blood transfusion and dialysis if required
- · there is no role for antibiotics, despite the preceding diarrhoeal illness in many patients
- the indications for plasma exchange in HUS are complicated.
 - As a general rule plasma exchange is reserved for severe cases of HUS not associated with diarrhoea
- Non-steroidal anti-inflammatory drugs and anti-diarrhoeals should be avoided

Prognosis

- Most children recover spontaneously from the illness, but mortality may be high in the elderly.
- Unfortunately fatality rates from HUS remain high, at between 5 and 10%.

MRCPUK- part-1- September 2012 exam: H/O bloody diarrhea and dehydration + ↓Platelet , ↑WBC, ↑urea & creatinine. Given the likely diagnosis, which organism is the most likely cause?

→ E. coli

MRCPUK- part-1- May 2010 exam: Feature of diarrhoea, lethargy & acute renal failure. There is a known local outbreak of E coli 0157:H7. Given the likely diagnosis, which one of the following investigation results would be expected?

→ Fragmented red blood cells (△ haemolytic uraemic syndrome)

Renal tubular defects

- · thick ascending limb of Henle's loop:
 - Bartter syndromes are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride in the thick ascending limb of Henle's loop
- distal convoluted tubule:
 - Gitelman syndrome are renal tubular salt-wasting disorders in which the kidneys cannot reabsorb chloride due to defect of thiazide-sensitive Na-CI cotransporter in the distal convoluted tubule
- proximal tubule:
 - Carbonic anhydrase is expressed in the proximal tubule and is inhibited by acetazolamide; this is manifested biochemically by normal anion-gap metabolic acidosis
 - Fanconi syndrome refers to a proximal tubular defect that results in wasting of phosphate, calcium and amino acids.
 - > seen in:
 - cystinosis
 - myeloma kidney
 - Wilson's disease
- collecting ducts :
 - Aquaporin channels are expressed in the cortical collecting ducts and are involved in water handling;
 - > defects result in diabetes insipidus

You may find it useful to remember the location of the nephron defects in these conditions as being alphabetical, i.e. Bartter affects the thick ascending limb, Gitelman affects distal tubule and Liddle syndrome affects the collecting ducts. BGL is in alphabetical order, as is the order of the affected location in the nephrons.

Fanconi syndrome

Pathophysiology

- Autosomal recessive
- Generalised dysfunction of the proximal tubule, with the resultant urinary loss of bicarbonate, calcium, phosphate, urate, amino acids, glucose, and other organic acids and bases.
- The proximal convoluted tubule cells are unable to reabsorb HCO3- leading to increased HCO3- excretion in the urine → Type 2 (proximal) renal tubular acidosis (RTA)

Causes

- · Inherited disorders
 - ⇒ Cystinosis (most common cause in children)
 - ⇒ Wilson's disease
 - ⇒ Type 1 glycogen storage disease
- Sjogren's syndrome
- Multiple myeloma
- Nephrotic syndrome
- Drugs: e.g. Rifampicin, Expired tetracycline antibiotics, aminoglycosides
- Heavy metal poisoning (e.g., lead, cadmium, mercury)
- Ischemia (acute tubular necrosis)
- Amyloidosis
- Vitamin D deficiency
- Paroxysmal nocturnal haemoglobinuria

Feature

- Polyuria, aminoaciduria, Glucosuria despite normal or low serum glucose
- Phosphaturia → Hypophosphatemia
- Hypouricemia
- In children → growth retardation, renal rickets
- Metabolic acidosis
- Osteomalacia

Treatment

- Replacement of lost electrolytes including potassium, phosphate, bicarbonate.
- · Treatment of the cause

Fanconi syndrome

- Renal proximal convoluted tubular dysfunction.
- Symptoms: Failure to thrive (poor growth), hypokalaemia (muscle weakness or spasms, fatigue, palpitations), and hypophosphatemia (rickets, abnormal growth).

Bartter and Gitelman syndromes

Definition

 Bartter and Gitelman syndromes are an autosomal recessive renal tubular defects result in hypokalemic salt-losing (ie, salt-wasting).

Pathophysiology |

- Gitelman syndrome: a loss of function mutation defect in thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule
- Bartter syndrome: a loss of function mutation defect in sodium chloride reabsorption in the thick ascending limb of Henle's loop (NKCC2)
- Hypokalemia, hypochloraemic metabolic alkalosis, polyuria, low to normal blood pressure, all result from impaired sodium chloride reabsorption.
- Renal biopsy → Hyperplasia of the juxtaglomerular apparatus is characteristic

Similar features (both Bartter and Gitelman)

- Often asymptomatic
- · fatigue, cramps and weakness.
- Salt craving, thirst, polydipsia, polyuria and nocturia.
- Normotensive hypokalaemic metabolic alkalosis
- ↑sodium loss in the urine →volume depletion, → ↑serum renin and aldosterone →
 potassium loss in the urine

Different features (which may differentiate Bartter from Gitelman)

- · Gitelman:
 - ⇒ most common,
 - ⇒ present in adolescence and early adulthood,
 - ⇒ has milder symptoms,
 - ⇒ pseudogout
 - ⇒ hypocalciuria
 - ⇒ severe hypomagnesemia.

Bartter:

- ⇒ present in children or early adolescence,
- ⇒ has more severe symptoms,
- ⇒ sensorineural deafness

- ⇒ hypercalciuria and normal or mild hypomagnesemia.
- ⇒ increased prostaglandin E₂ (PGE₂) production

Diagnosis approach

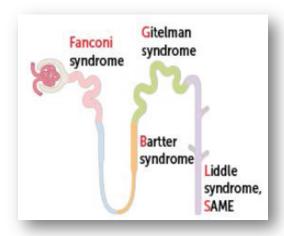
- Step 1: suspicion: Bartter or Gitelman syndrome should be suspected in any patient with unexplained hypokalemia, metabolic alkalosis, and a normal or low blood pressure.
- Step 2 : exclude other more common causes of these findings, in particular diuretic and/or laxative abuse and surreptitious vomiting → Urine diuretic screen.
- **Step 3**: spot urine chloride (repeated several times)
 - ⇒ consistently high (>20 mEq/L) in Bartter and Gitelman syndromes.
 - ⇒ consistently low (<20 mEq/L) with vomiting
 - ⇒ fluctuates between low and high with intermittent (and surreptitious or denied) diuretic use (high when the diuretic effect is present and low when it dissipates).
- Step 4: genetic testing

Distinguishing Bartter syndrome from Gitelman syndrome

	Gitelman syndrome	Bartter syndrome
Gene affected	SLC12A3	SLC12A1
		(Bartter syndrome type I)
prevalence	1 in 40,000	1 in a million.
Site of defect	Thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule	Sodium chloride reabsorption in the thick ascending limb of Henle's loop (NKCC2)
Presentation	present in adolescence and early adulthood (milder symptoms)	Most cases are discovered in infancy or early adolescence (more severe symptoms)
Concentrating and diluting abilities	Concentrating capacity normal/near normal and diluting capacity reduced	Concentrating capacity reduced and diluting capacity reduced
Urinary calcium	Reduced (hypocalciuria)	Increased (hypercalciuria)
Serum magnesium	severe hypomagnesemia is common	either normal or mildly reduced

Treatment (for Bartter or Gitelman syndrome)

- First line: Electrolyte supplementation (sodium, potassium, and magnesium salts)
- Second line: Potassium-sparing diuretics that inhibits distal sodium-potassium exchange, such as spironolactone, eplerenone, or amiloride.
- Third-line: NSAIDs or ACE inhibitors



Locations of renal tubular defects

SAME: Syndrome of Apparent Mineralocorticoid Excess

The effects of Gitelman syndrome are similar to those of a thiazide diuretic. The effects of Bartter syndrome are similar to those of a loop diuretic. Loop diuretics work by inhibiting NKCC2- Think of Barters syndrome as like taking large dose of furosemide.

Gitelman's syndrome: Normotensive hypokalaemic metabolic alkalosis with Hypocalciuria and significant hypomagnesaemia.

Bartter syndrome: Normotensive hypokalaemic metabolic alkalosis with hypercalciuria, normal or mild hypomagnesaemia, metabolic alkalosis.

The hypokalemia with normal blood pressure in a middle aged male without any skeletal abnormalities or retardation would suggest a diagnosis of Gitelman syndrome rather than Bartter's syndrome.

Renal tubular defects

	Causes	Defect	Effect	Note
Bartter syndrome	Autosomal recessive	Reabsorption defect in thick ascending loop of Henle (affects Na+ /K+/2 Cl – cotransporter)	Normotensive hypokalaemic metabolic alkalosis hypercalciuria	Presents similarly to chronic loop diuretic use
Gitelman syndrome	Autosomal recessive	Reabsorption defect of NaCl in distal convoluted tubule	Normotensive hypokalaemic metabolic alkalosis, hypomagnese mia, hypocalciuria	Presents similarly to life-long thiazide diuretic use Less severe than Bartter syndrome
Liddle syndrome	Autosomal dominant	Gain of function mutation → ↓Na+ channel degradation → ↑Na+ reabsorption in collecting tubules	Hypertensive hypokalaemic metabolic alkalosis, ↓aldosterone	Presents similarly to hyperaldosteronism, but aldosterone is nearly undetectable. Treatment: amiloride
Fanconi syndrome	Hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease), ischemia, multiple myeloma, nephrotoxins/drug s (eg, cisplatin), lead poisoning	Generalized reabsorption defect in PCT excretion of amino acids , glucose, HCO3 –, and PO43 –, and all substances reabsorbed by the PCT	Hypokalemic metabolic acidosis (proximal RTA), hypophosphat emia	Growth retardation and rickets/ osteopenia common due to hypophosphatemia Volume depletion also common
Syndrome of Apparent Mineralo- cortid Excess (SAME)	Autosomal recessive OR acquired from glycyrrhetinic acid (present in liquorice), which blocks activity of 11β-hydroxy steroid dehydrogenase	Cortisol activates mineralocorticoid receptors;11β-HSD converts cortisol to cortisone (inactive on these receptors) Hereditary 11β-HSD deficiency →↑cortisol →↑mineralocorticoi d receptor activity	Hypertensive hypokalaemic metabolic alkalosis, ↓aldosterone, Cortisol tries to be the SAME as aldosterone	Treatment: K+- sparing diuretics (↓mineralocorticoid effects) or corticosteroids (exogenous corticosteroid →↓ endogenous cortisol production →↓ mineralocorticoid receptor activation)

Liddle's syndrome

Pathophysiology 1 4 1

Autosomal dominant (gain of function mutation) → ↑ activity of Epithelial Sodium
 Channels (ENaC) → ↑ reuptake of water and sodium → activation of sodium/potassium
 exchange independent of circulating mineralocorticoid (pseudohyperaldosteronism).

Diagnostic features

- Hypertension
- Hypokalaemia
- Metabolic alkalosis
- · Decreased renin and aldosterone levels

Treatment

- Amiloride: Potassium-sparing diuretics: acts directly on the sodium channel →
 (epithelial sodium channel (ENaC) antagonists)
- Spironolactone is not an effective treatment as the increased activity of the ENaC is not mediated by aldosterone.

Top Tips

Liddle's syndrome: hypokalaemia + hypertension

hypokalaemic alkalosis + suppressed renin and aldosterone + hypertension \rightarrow Liddle's syndrome

The clinical features of Liddle syndrome are similar to those of hyperaldosteronism, except that Liddle syndrome manifests with decreased renin and aldosterone levels.

Glomerulonephritides

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

Membranous glomerulonephritis

- presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- cause: infections, rheumatoid drugs, malignancy
- 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease

IgA nephropathy - aka Berger's disease, mesangioproliferative GN

typically young adult with haematuria following an URTI

Diffuse proliferative glomerulonephritis (DPGN)

Diffuse proliferative glomerulonephritis, causes:

- post-streptococcal
- SLE

Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients

- classical post-streptococcal glomerulonephritis in child
- presents as nephritic syndrome / acute kidney injury
- The following features are supportive of diagnosis:
 - haematuria
 - proteinuria
 - oedema
 - hypertension
- most common form of renal disease in SLE
- In DPGN, more than 50% of the glomeruli (diffuse) show an increase in mesangial, epithelial, endothelial (proliferative), and inflammatory cells (ie, glomerulonephritis). (Increased cellularity)
- when < 50% of the glomeruli are involved, the condition is termed focal proliferative glomerulonephritis. However, this entity has the potential to progress to DPGN.

Minimal change disease

- typically a child with nephrotic syndrome (accounts for 80%)
- · causes: Hodgkin's, NSAIDs
- · good response to steroids

Focal segmental glomerulosclerosis

- may be idiopathic or secondary to HIV, heroin
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease

Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis

- rapid onset, often presenting as acute kidney injury
- · causes include Goodpasture's, ANCA positive vasculitis

Mesangiocapillary glomerulonephritis (membranoproliferative)

- type 1: cryoglobulinaemia, hepatitis C → associated with low C4
- type 2: partial lipodystrophy → associated with low C3
- C3 nephritic factor is an autoantibody specific for alternative pathway C3 convertase (C3NeF), found in mesangiocapillary GN type II and partial lipodystrophy.

Diagnosis

- Renal biopsy is the best investigation to diagnose Glomerulonephritis
- RBC casts in urinary sediment suggest a diagnosis of acute glomerulonephritis (Acute nephritic syndrome)
- Immune complex glomerulonephritides can be classified based on normal or decreased C³.
 - Associated with reduced C³ and C⁴
 - Cryoglobolinaemia
 - Infective endocarditis
 - lupus nephritis
 - Associated with reduced C³
 - membranoproliferative GN
 - post-streptococcal GN

Glomerulonephritis and low complement Disorders associated with

glomerulonephritis and low serum complement levels:

- 1. post-streptococcal glomerulonephritis
- 2. subacute bacterial endocarditis
- 3. systemic lupus erythematosus
- 4. mesangiocapillary glomerulonephritis

MRCPUK-part-1-May 2014 exam: A patient of SLE present with pedal oedema, ↑ BP. Dipstick urine shows protein ++, blood+++.What is the renal biopsy most likely to show?

→ Diffuse proliferative glomerulonephritis (Diffuse proliferative glomerulonephritis is the most common and severe form of renal disease in SLE patients.)

Minimal change disease

Minimal change glomerulonephritis - prednisolone

Nephrotic syndrome in children / young adults - minimal change glomerulonephritis

Epidemiology

- accounting for 75% of cases in children and 25% in adults.
- · peak incidence 2-3 years of age

Causes

- 90% of cases are idiopathic
- Other causes (10 20%)
 - drugs: NSAIDs, rifampicin gold and lithium
 - > Hodgkin's lymphoma, thymoma
 - infectious mononucleosis

Pathophysiology

- The glomerular basement membrane is normal on electron microscopy
- T-cell and cytokine mediated damage to the glomerular basement membrane → polyanion loss
- the resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin

Features

- nephrotic syndrome
 - nearly always presents as nephrotic syndrome
- normotension
 - hypertension is rare (only 10%)
- highly **selective proteinuria*** (*only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus)
 - ⇒ A protein selectivity index of less than 10% is highly selective and is a ratio of serum and urine IgG and albumin.
 - ⇒ High selectivity suggests minimal change disease but is less reliable in adults.
- Renal biopsy:
 - > light microscopy are normal or small looking glomeruli
 - electron microscopy shows fusion of podocytes

- (Effacement of the epithelial cell foot processes over the outer surface of the GBM)
- renal biopsy is not indicated unless no response to steroids is seen within one month, there is hypertension, haematuria or renal impairment.
 - renal biopsy is usually only attempted when three or more episodes of oedema have occurred.

Podocytes fusion is seen in minimal change glomerulonephritis but may occasionally be a feature of focal segmental glomerulosclerosis as well. Minimal change however is far more common

Management

- majority of cases (80%) are steroid responsive
 - shows excellent response to steroids since the damage is mediated by <u>T- cell</u> cytokines.
- cyclophosphamide is the next step for steroid resistant cases
 - Immunosuppression treatment (cyclophosphamide) should be considered in patients who are frequent relapsers (two or more episodes in six months of the initial response, or four relapses in any one year, children who are steroid dependent or steroid toxic).

Prognosis is overall good

- · Remission: Full renal recovery is the most likely outcome.
 - > In Children:
 - 30 40% of children achieve spontaneous remission
 - and 90% achieve remission following eight weeks treatment with high dose steroids.
 - > In adults only around 50% achieve remission.
- Relapse is common. Roughly:
 - ➤ 1/3 have just one episode
 - > 1/3 have infrequent relapses
 - > 1/3 have frequent relapses which stop before adulthood

Membranous glomerulonephritis

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

- Membranous glomerulonephritis is the commonest type of glomerulonephritis in adults and is the third most common cause of end-stage renal failure (ESRF).
- It usually presents with nephrotic syndrome or proteinuria.
- It is an antibody mediated disease in which the immune complexes localise to the subepithelial aspect of the capillary loop. That is, between the outer aspect of the basement membrane and the podocyte (epithelial cell).
- Males are twice as commonly affected as females
- Typically seen in the over 40 age group (Elderly patients)
- Most patients have normal blood pressure at the time of the presentation.

Most of the patients with membranous glomerulonephritis have antibodies against <u>M-type</u> phospholipase A2 receptor.

Causes

- idiopathic
- infections: hepatitis B, hepatitis C, malaria, syphilis, leprosy, HIV, schistosomiasis,
- malignancy: lung cancer, non-Hodgkin's lymphomas lymphoma, leukaemia, colon and gastric cancer
 - (30% of membranous nephropathy cases are secondary, of those around a third (10% of the total cases of membranous nephropathy) are diagnosed with an underlying malignancy)
 - (NOTE: In the case of Hodgkin's lymphoma, the most common histological type of renal involvement is minimal change glomerulonephritis followed by focal segmental glomerulosclerosis).
- drugs: gold, penicillamine, NSAIDs, captopril, and heavy metals: mercury and cadmium
- autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid
- Sickle cell disease.
- · Diabetes mellitus.

Renal biopsy demonstrates:

- · light microscopy:
 - diffuse capillary and glomerular basement membrane thickening.
- electron microscopy:
 - the basement membrane is thickened with subepithelial electron dense deposits (Thickened capillary loops). This creates a 'spike and dome' appearance
- Immune complex
 - deposition with IgG and C3

Complications

- Renal vein thrombosis is particularly likely to complicate membranous glomerulonephritis
 - As the left testicular vein drains into the left renal vein, a left-sided varicocele may develop in this condition.

Prognosis

- Rule of thirds
 - > one-third: spontaneous remission
 - > one-third: remain proteinuric
 - > one-third: develop ESRF
- Good prognostic features include:
 - female sex
 - young age at presentation and
 - asymptomatic proteinuria of a modest degree at the time of presentation.

Management:

- Immunosuppression: corticosteroids alone have not been shown to be effective.
- A combination of corticosteroid + another agent such as chlorambucil is often used
 - Cyclophosphamide plus methylprednisolone is the most appropriate management
- blood pressure control: ACE inhibitors have been shown to reduce proteinuria

- Ramipril is proven to affect both proteinuria and hypertension in patients with a diagnosis of membranous nephropathy, and is therefore the most likely treatment to affect the patient's prognosis
- · consider anticoagulation
- Approximately 30% of cases are secondary to other conditions, and in those cases treatment of the underlying cause may be curative.

MRCPUK-part-1-September 2011 exam: H/O colorectal cancer developed 'frothy' urine. The results suggest nephrotic range proteinuria. Assuming the proteinuria is related to his colorectal cancer what is the renal histology most likely to show?

→ Membranous glomerulonephritis

MRCPUK-part-1-May 2012 exam: H/O peripheral oedema with no past medical history of note. His urinary protein is 4.2g/24 hours. BP is 160/92 mmHg. A renal biopsy shows: thickened capillary walls& Subepithelial deposits. Given the likely diagnosis, which one of the following drugs is most likely to be beneficial?

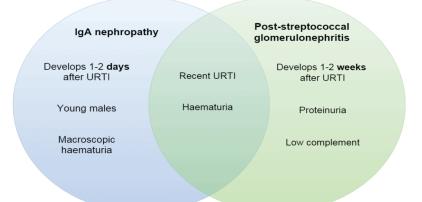
→ ACE inhibitor (∆ membranous glomerulonephritis)

IgA nephropathy

Basics

- also called Berger's disease or mesangioproliferative glomerulonephritis
- commonest cause of glomerulonephritis worldwide
- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)
- Has a male preponderance
- commonly diagnosed in the age range of 20-40.

Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis



- post-streptococcal glomerulonephritis is associated with low complement levels
- main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur)
- there is typically an interval between URTI and the onset of renal problems in poststreptococcal glomerulonephritis

Presentations

- young male, recurrent episodes of macroscopic haematuria
- Haematuria occurs within 12-24 hours of pharyngitis.

- typically associated with mucosal infections e.g., URTI, or less commonly infection of other mucous membranes (e.g. GI, bladder, breast).
- accompanied also by loin pain, muscle pain and fever.
- · nephrotic range proteinuria is rare
- The majority of patients have normal renal function.
- renal failure

Associated conditions

- Alcoholic cirrhosis (Alcohol excess) (haematuria + alcohol excess → IgA nephropathy).
- · coeliac disease/dermatitis herpetiformis
- Henoch-Schonlein purpura

Diagnosis

- Renal biopsy is the investigation of choice to confirm the diagnosis
 - histology: Mesangial hypercellularity,
 - positive immunofluorescence for IgA & C3

Management

- No specific treatment is available. Observation is the most appropriate management
- steroids/immunosuppressants not be shown to be useful.
 - > Treatment with corticosteroids is usually reserved for those patients with hypertension and a rising creatinine.
- When there is nephrotic range proteinuria (>3 g/day) an 8-12 week course of prednisolone should be prescribed.
- If the proteinuria is <3 g/day an ACE inhibitor can be used.

Prognosis

- 30% of children will have a spontaneous remission within 10 years
- 25% of patients develop ESRF within 20 years
- · markers of good prognosis: frank haematuria
- · markers of poor prognosis:
 - > male gender,
 - proteinuria (especially > 2 g/day),
 - hypertension
 - > smoking,
 - hyperlipidaemia,
 - > ACE genotype DD

MRCPUK-part-1-September 2011 exam: A 17-year-old man with several episodes of visible haematuria. occurs within a day or two of URTI. Urine dipstick is normal. What is the most likely diagnosis?

→ IgA nephropathy

MRCPUK-part-1-January 2006 exam: A 10-year-old boy with past two days H/O sore throat associated with blood in his urine. glomerulonephritis is suspected. What would a renal biopsy most likely show?

→ Mesangial hypercellularity (∆ lgA nephropathy)

MRCPUK-part-1-September 2007 exam: A 12-year-old boy with purpuric rash on the extensor surfaces of his lower legs + abdominal pain and an urticarial rash. Urine dipstick reveals blood ++.What would be the likely finding on renal biopsy?

→ Mesangial hypercellularity (Henoch-Schonlein purpura is associated with IgA nephropathy)

MRCPUK-part-1-January 2014 exam: A 19-year-old woman C/O painless visible haematuria, occur within a day or two of developing tonsillitis. BP is 148/90 mmHg. Given the likely diagnosis, which marker indicate poor prognosis?

→ Hypertension (∆ IgA nephropathy)

MRCPUK-part-1-September 2007 exam: Which one of the following is associated with a better prognosis in patients with IqA nephropathy?

→ Frank haematuria

Post-streptococcal glomerulonephritis

Overview

- Also known as acute proliferative glomerulonephritis
- typically occurs 7-14 days following a group A beta-haemolytic *Streptococcus* infection (usually *Streptococcus pyogenes*).
 - ➤ Acute glomerulonephritis can be caused by both pharyngeal and skin infections with group A beta-haemolytic Streptococcus, but only pharyngeal infections typically lead to acute rheumatic fever.
- caused by immune complex (IgG, IgM and C3) deposition in the glomeruli.
- type III hypersensitivity reaction.

Epidemiology

Young children most commonly affected.

Features

- · general: headache, malaise
- haematuria
 - Dark-colored urine is often a presenting sign.
- · nephritic syndrome
- hypertension

Investigations

- BMP (Basic metabolic panel)
 - > the most important step in the diagnosis
 - > BMP to evaluate serum **creatinine** kidney function is ideal to determine the level of glomerulonephritis in this patient and guide treatment.
- low C3
- normal C4 level or only slightly reduced, indicating activation of the alternate complement pathway
- Depressed CH 50 level
- Raised ASO titer
- Renal biopsy
 - post-streptococcal glomerulonephritis causes acute, diffuse proliferative glomerulonephritis
 - endothelial proliferation with neutrophils
 - electron microscopy:
 - subepithelial 'humps' caused by lumpy immune complex deposits.
 - The hump-like appearance in subepithelial space is characteristic of post-streptococcal glomerulonephritis.
 - 'Lumpy-bumpy' appearance on immunofluorescence is characteristic.
 - immunofluorescence:
 - granular or 'starry sky' appearance
 - There is antibody and compliment deposition on immunostaining.

- > light microscopy
 - 'wire-loop' lesions on light microscopy.

Treatment

• Patients with acute proliferative glomerulonephritis presenting with hypertension are managed with loop diuretics.

Prognosis

- Carries a good prognosis
- Age is the most important prognostic factor in post-streptococcal glomerulonephritis.
 - ▶ 95% of affected children recover completely, compared with 25% of adults over 60 years old.

Membrano-proliferative glomerulonephritis (MPGN).

Membranoproliferative glomerulonephritis (mesangiocapillary)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

Overview

- also known as mesangio-capillary glomerulonephritis(MCGN),
- more recently been termed complement mediated glomerulonephritis.

Associations

 It is associated with SLE, cryoglobulinaemia with or without hepatitis C, chronic infections (SBE), neoplasms, hepatitis B, schistosomiasis, malaria and leprosy.

General features

- may present as nephrotic syndrome, haematuria or proteinuria
- · Circulating immune complexes are seen
- Classically associated with decreased serum C3 (and a normal C4, indicating activation of the alternative pathway of complement).
- Hypocomplementemia (Low C3 levels) is a characteristic finding with all types of (MPGN).
- appears on light microscopy with "tram-track" capillary loops of glomerular basement membranes.

Type 1

- Epidemiology
 - accounts for 90% of cases
- histology
 - <u>sub-endothelial</u> immune deposits of electron dense material, <u>Thickening and splitting of the capillary basement membrane</u> (double layer of glomerular basement membrane), resulting in a 'tram-track' appearance
- · Causes:
 - - hepatitis C
 - (hepatitis C is endemic among the iv drug-users).
 - Hepatitis C is now considered the principal cause of 'idiopathic' mesangiocapillary glomerulonephritis (MCGN),

Type 2

- Also known as → Dense deposit disease
- causes:
 - partial lipodystrophy,
 - factor H deficiency,
 - may be idiopathic or

> may occur after measles

- Features
 - > reduced serum complement
 - ➤ C3b nephritic factor (an antibody against C3bBb) found in 70% → low C3
- Histology
 - 'dense deposit'
 - > characterised by mesangial cell proliferation with electron-dense,
 - linear intramembranous deposits that stain positive for C3 (C3 nephritic factor)

Type 3

- · Subepithelial and subendothelial deposits
- · causes: hepatitis B and C

Management

· steroids may be effective

Prognosis

· poor prognosis

MRCPUK-part-1-September 2009 exam: patient of nephrotic syndrome is noted to have marked loss of subcutaneous tissue from the face. What is the most likely underlying cause of her renal disease?

→ Membranoproliferative glomerulonephritis type II (△ partial lipodystrophy)

MRCPUK-part-1-September 2009 exam: A patient develops membranoproliferative glomerulonephritis secondary to partial lipodystrophy. Which type of complement is likely to be low?

→ C3

Rapidly progressive glomerulonephritis (RPGN)

Rapidly progressive glomerulonephritis, causes:

- Goodpasture's
- ANCA positive vasculitis

Overview

- rapid loss of renal function associated with the formation of epithelial crescents in the majority of glomeruli.
- results in a rapid decrease in GFR of at least 50% over a short period (a few days to 3 months).
- The most aggressive GN, with potential to cause ESRF over days.

Causes

- Goodpasture's syndrome
- Wegener's granulomatosis
- others: SLE, microscopic Polyarthritis
- · secondary syphilis

Types

- 1. Type I RPGN (~3%):
 - > Serum anti-glomerular basement membrane (Anti-GBM) antibody is positive.
 - > Antibody deposits along the glomerular basement membrane in a linear fashion.
 - > Example: Goodpasture syndrome.
- 2. Type II RPGN: Immune complex disease (~45% of cases):
 - > (Anti-GBM) antibody is negative,

- but irregular immune complex (antibody-antigen) deposits are found within the glomeruli.
- Example: lupus nephritis and post-streptococcal glomerulonephritis.
- 3. Type III RPGN: (Pauci-immune disease (~50% of cases, 80–90% ANCA +ve):
 - Serum anti-neutrophil cytoplasmic (ANCA) antibodies are positive.
 - > Negative immunofluorescence.
 - > Example: Wegener granulomatosis and microscopic polyangiitis.

Features

- nephritic syndrome: haematuria with red cell casts, proteinuria, hypertension, oliguria
- features specific to underlying cause (e.g. haemoptysis with Goodpasture's, vasculitic rash or sinusitis with Wegener's

Investigations

- Immunofluorescence detects deposits of IgG and C3 in the glomerular BM
- The main pathological finding is fibrinoid necrosis > 90% of biopsy specimens with
 extensive crescent formation in at least 50% of the glomeruli. These crescents are
 collections of epithelial cells and macrophages proliferation within the Bowman's space.

Treatment

- Aggressive immunosuppression with high-dose IV steroids and cyclophosphamide
- +/- plasma exchange.

Prognosis:

• 5-year survival 80%.

MRCPUK-part-1-January 2012 exam: H/O chronic sinusitis, haemoptysis and microscopic haematuria. cANCA (PR3)= Positive. Given the likely diagnosis, what findings would be expected on renal biopsy?

→ Crescentic glomerulonephritis

Focal segmental glomerulosclerosis (FSGS)

Overview

- cause nephrotic syndrome and chronic kidney disease.
- In FSGS, as the name suggests, only some glomeruli are affected (focal) and just some of the affected glomeruli are diseased (segmental).
- <u>cholesterol levels rise</u> due to increased cholesterol synthesis in the liver and the loss of lipid-regulating proteins in urine

Epidemiology

- · generally presents in young adults.
- the second most common cause of nephrotic syndrome in adults, after membranous glomerulonephritis (GN)
- The most common cause of nephrotic syndrome in Hispanic and African-Americans
- Incidence: 40% in adults. 20% in children

Pathophysiology

• Caused by an injury to **podocytes** in the renal glomeruli.

Causes

- idiopathic (in 80%)
- secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- HIV→ 'collapsing glomerulopathy'
 - > The most common type of (HIV-associated nephropathy) is a collapsing (FSGS).
- intravenous drug use

- heroin
- · Alport's syndrome
- sickle-cell
- associated with severe obesity
- medications:
 - > Interferon alfa, lithium, sirolimus, and pamidronate.

Histology

- histology <u>may</u> appear normal and may be confused with minimal change nephropathy
- deep glomeruli at the corticomedullary junction are affected first, these may be missed on transcutaneous biopsy, leading to a <u>mistaken diagnosis of a minimal change</u> glomerular lesion
- light microscopy
 - Segmental sclerosis and hyalinosis
- Immunofluorescence microscopy
 - usually unremarkable.
 - ➤ Immunofluorescence is negative because there is no antibody or immune complex deposition.
 - > biopsy will show partial scarring of the glomerulus with no immunofluorescence.
- Electron microscopy
 - ➤ The hallmark pathologic feature is <u>podocyte foot processes</u> fusion.
 - can distinguish primary from secondary FSGS. Foot process fusion is diffuse in primary FSGS but is mostly limited to sclerotic areas in secondary FSGS.
- fibrinogen are deposited in juxtamedullary capillaries

Treatment

- 50% of (FSGS) do not respond to steroid
- The first line of management is glucocorticoids.
- (ACE) inhibitors are a recognised strategy to slow the progression of renal disease.

Prognosis

- It leads to chronic renal failure in 50% of cases.
- typically progresses to renal failure over a 6–8 year period.
- 2% of dialysis patients have FSGS.
- have a high recurrence rate in renal transplants
 - > FSGS recurs in 40% of renal transplants

January 2011 exam: A patient with H/O heroin abuse, his creatinine = 156, urine show = ++ protein. What is the most likely cause of his deteriorating renal function?

→ Focal segmental glomerulosclerosis (Heroin is a known cause of focal segmental glomerulosclerosis)

Goodpasture's syndrome

Goodpasture's syndrome

- IgG deposits on renal biopsy
- anti-GBM antibodies

Goodpasture's syndrome is characterised by pulmonary haemorrhage and crescentic glomerulonephritis.

Definition

 Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis.

Epidemiology

- more common in men (sex ratio 2:1)
- has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket).

Genetics

- associated with HLA DR2
- p-ANCA positive in 30% and is directed against myeloperoxidase.

Pathophysiology

- It is a type II cytotoxic reaction caused by anti-glomerular basement membrane (anti-GBM) antibodies against the α 3 chain of type IV collagen (basement membrane of both the kidneys and lungs).
- Goodpasture syndrome is due to IgG antibodies produced against the basement membrane causing damage via a type II hypersensitivity reaction.

Features

- · pulmonary haemorrhage
 - respiratory symptoms can vary from minimal hemoptysis to massive alveolar hemorrhage, leading to respiratory failure. In lungs, this is a type 2 hypersensitivity reaction.
 - Hemoptysis is a clinical feature of Goodpasture's syndrome due to <u>cross</u>
 reaction of anti-glomerular basement membrane antibodies at the lungs.
 - > cough
 - > Fever
- followed by rapidly progressive glomerulonephritis (RPGN) (Renal impairment is caused by a **crescentic glomerulonephritis**)
 - haematuria
 - > proteinuria, and
 - red cell casts.

Factors which increase likelihood of pulmonary haemorrhage

- normally, the alveolar epithelium prevents contact of antibody with basement membrane collagen, thus any condition that increases permeability of alveoli can cause triggering of this syndrome. Such susceptibility factors include:
 - smoking
 - lower respiratory tract infection
 - > pulmonary oedema
 - inhalation of hydrocarbons and toxic gases
- young males

Investigations

- serological testing (for anti-GBM antibodies)
- biopsy from kidney rather than lung.
 - Renal biopsy:
 - linear IgG deposits along basement membrane (the most likely finding on renal biopsy → Linear immunofluorescence)
 - Lung biopsy
 - linear staining of IgG along the alveolar capillary basement membranes

- disruption of alveolar septa and haemosiderin-laden macrophages because there may be pulmonary haemorrhage associated with the condition.
- raised transfer factor secondary to pulmonary haemorrhages.
- Serial measurement of carbon monoxide (CO) diffusing capacity or transfer factor (Tlco) can be used to monitor progression,

Management

- · General management
 - > ABC
 - If the patient is hypoxic → intubate and mechanically ventilate the patient.
 - Patients should not smoke and should avoid hydrocarbon exposure.
- The most appropriate <u>initial management</u> → IV methylprednisolone and cyclophosphamide
- plasma exchange (plasmapheresis)
 - Where there is severe haemoptysis, rapid removal of anti-GBM antibody is indicated, and the best way to do this is by plasmapheresis at a specialist centre.
 - > This is usually accompanied by pulsed therapy with IV methylprednisolone and cyclophosphamide.
- steroids
- cyclophosphamide
 - Response is assessed by monitoring symptoms and anti-GBM antibody titres.
 - Cyclophosphamide and prednisolone continued, typically for 6 9 months following remission.

In the acute setting, treatment is focused on:

- managing life threatening complications of renal failure, such as hyperkalaemia → haemodialvsis.
- Removing the circulating auto-antibody responsible for disease → plasmapharesis (therapeutic plasma exchange),
 - the most important management step in the next few days after haemodialysis

Prognosis:

- Despite treatment, the **mortality** of Goodpasture's is 11% and it has a high **morbidity** with 60% of patients becoming dependent on dialvsis.
- In practice, glomerulonephritis proves to be a much commoner threat to survival than lung haemorrhage.

Other causes of raised anti-GBM antibody levels:

- Some healthy individuals exposed to inhaled oils, hydrocarbons or solvents can have borderline raised anti-GBM antibody levels.
- Anti-GBM antibodies have also been detected in HIV-negative patients with Pneumocystis pneumonia.

Nephrotic syndrome

Triad of:

- 1. Proteinuria (> 3g/24hr) (The minimum proteinuria which is defined as 'nephrotic' is 300 mg/mmol) causing →
- 2. Hypoalbuminaemia (< 30g/L) and
- 3. Oedema

Other features:

- Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels
 predispose to thrombosis.
- Loss of thyroxine-binding globulin lowers the total, but not free, thyroxine levels.
- Increased serum cholesterol
 - > ↑(LDL)
 - LDL and VLDL are removed from serum by lipoprotein signals. If the lipoprotein is lost in the urine with nephrotic syndrome, then the lipid levels in the blood rise.
 - HDL is usually normal
- ↓↓ Ca & vit D (loss of 25-hydroxyvitamin D3 (25OHD3) in the urine → hypocalcaemia)
- Serum C3 levels are decreased in immune complex-mediated glomerulonephritis

	Nephrotic	Nephritic
Common primary causes	Membranous Minimal change FSGS Mesangiocapillary GN	IgA nephropathy Mesangiocapillary GN
Common secondary causes	Diabetes SLE (class V nephritis) Amyloid Hepatitis B/C	Post streptococcal Vasculitis SLE (other classes of nephritis) Anti-GBM disease (Figs 1 & 2) Cryoglobulinaemia
ВР	Normal–mild ↑	Moderate-severe ↑
Urine	Proteinuria >3.5g/day	Haematuria (mild-macro)
GFR	Normal–mild ↑	Moderate–severe ↓

Causes

Nephrotic syndrome - malignancies cause membranous glomerulonephritis

- glomerulonephritis accounts for around 80% of cases
 - minimal change glomerulonephritis (causes 80% in children, 30% in adults)
 - > membranous glomerulonephritis
 - focal segmental glomerulosclerosis (FSGS).
 - Patients presenting with isolated heavy proteinuria without the other components of nephrotic syndrome is more likely due to (FSGS).
 - membranoproliferative glomerulonephritis
- Systemic disease (about 20%)
 - > diabetes mellitus
 - (Diabetic nephropathy often presents as nephrotic syndrome but typically develops at least 15 years after onset).
 - > systemic lupus erythematosus
 - amyloidosis (in patient with chronic inflammatory state, amyloidosis is the likely cause of NS)

- Drugs
 - gold (sodium aurothiomalate), penicillamine
- Others
 - congenital
 - > neoplasia: carcinoma, lymphoma, leukaemia, myeloma
 - Chronic lymphocytic leukemia (CLL) and Non-Hodgkin's lymphoma (NHL) are the most common hematologic malignancies associated with glomerular diseases
 - Membranoproliferative glomerulonephritis (MPGN) are most common glomerular disease associated with CLL and NHL
 - the most common renal lesion associated with Hodgkin's disease is minimal change disease
 - infection: bacterial endocarditis, hepatitis B, malaria (commonly plasmodium malariae)

Investigations

- Renal biopsy
- Contraindications for renal biopsy:
 - Abnormal clotting
 - Hypertension >160/>90mmHg
 - Single kidney (except for renal transplants)
 - Chronic kidney disease with small kidneys (<9cm)</p>
 - Uncooperative patient
 - Horseshoe kidney
 - Renal neoplasms.

Serum electrophoresis in nephrotic syndrome

- ↑ serum α- and β-globulin fractions. (The increase in globulin fractions is thought to
 occur due to increased synthesis in patients with urinary protein loss)
 - > Increased α1 and α2-globulin fractions, decreased serum albumin
- A monoclonal paraprotein band will be present where myeloma is the underlying cause.
- there may be associated immune paresis with reduced concentrations of one or more of the immunoglobulins IgG, IgA or IgM

Complications

- increased risk of infection in particular pneumococcal infections due to urinary immunoglobulin loss and decreased splanchnic blood flow.
- Increased risk of thromboembolism related to loss of antithrombin III and plasminogen in the urine, increased fibrinogen and increased factor VIIIc. Renal vein thrombosis occurs in 15-20% of patients with nephrotic syndrome
 - Renal vein thrombosis
 - Occurs in 10-20%
 - Feature → often clinically silent , (loin pain + haematuria) and acute renal injury
 - Initial investigation → US (swollen oedematous kidney)
 - Diagnosis → Duplex US renal veins, CT or MRV
 - Treatment → long term anticoagulation.
- hyperlipidaemia
- hypocalcaemia (vitamin D and binding protein lost in urine)
- acute renal failure
- Intravascular volume depletion: Hypoalbuminaemia results in decreased intravascular oncotic pressure, leading to leakage of extracellular fluid from blood to the interstitium

Treatment

- In general, steroids are tried first and then second line agents such as cyclosporin and cyclophosphamide are introduced if needed.
- Cyclophosphamide is the best treatment for steroid-dependent nephrotic syndrome
 - No more than two courses of cyclophosphamide should be prescribed in children because of the risk of side effects, which include azoospermia
 - An alternative to cyclophosphamide is ciclosporin, which is effective but must be continued long-term to prevent relapse on stopping treatment. Ciclosporin is also potentially nephrotoxic

MRCPUK-part-1-January 2006 exam: What changes in patients with nephrotic syndrome predispose to the development of venous thromboembolism?

→ Loss of antithrombin III

Which finding would support a diagnosis of a protein losing enteropathy rather than nephrotic syndrome?

- → Low total cholesterol
 - The pathophysiology of protein loss in protein-losing gastroenteropathy is different from that in glomerular diseases.
 - In glomerulopathies, protein loss is determined by molecular weight and charge.
 - By contrast, the leakage of individual serum proteins in patients with proteinlosing gastroenteropathy is independent of molecular weight.
 - For this reason, cholesterol levels are low, in contrast to nephrotic syndrome where cholesterol levels are high (due to the molecular weight of cholesterol).

Analgesic nephropathy

- common in women, F: M = 2: 1, and presents most often in middle age
- caused by non-steroidal anti-inflammatory drugs (NSAIDs) for chronic pain or headache,
- Characteristically, associated with phenacetin use, particularly in Australia and New Zealand
- features may include anaemia, chronic renal failure, symptoms of urinary tract infection, haematuria or hypertension.
- Complications
 - > Urinary tract malignancy (8-10% of patients with analgesic nephropathy),
 - > For example, in women under the age of 50 analgesic abuse is the most common cause of bladder cancer.

Renal stones

Renal stones on x-ray

- · cystine stones: semi-opaque
- urate + xanthine stones: radio-lucent

Stag-horn calculi

- composed of Struvite (ammonium magnesium phosphate, triple phosphate)
- form in alkaline urine (ammonia producing bacteria such as Ureaplasma urealyticum and Proteus therefore predispose)
- The most common stones are calcium oxalate stones followed by calcium phosphate.
- Calcium phosphate stones are seen in renal tubular acidosis (RTA).

Risk factors

- dehydration
- hypercalciuria, hyperparathyroidism, hypercalcaemia
- cystinuria (AR defect in dibasic amino acid transporter)
- high dietary oxalate. hyperoxaluria (for example, XS intake, ileal disease and bypass)
- renal tubular acidosis => (Calcium phosphate stones)
- · medullary sponge kidney, polycystic kidney disease
- · beryllium or cadmium exposure
- Chronic infection with urea splitting organisms: causes stones made of magnesium ammonium phosphate and calcium phosphate (infection stones (5%)
- Familial: Idiopathic hypercalciuria inherited as autosomal dominant whereas cystinuria, cystinosis, urate uropathy and hyperoxaluria are autosomal recessive conditions.
 - > the most common cause being increased gastrointestinal (GI) absorption of calcium.
 - > The most common stones are calcium oxalate stones.
 - there appears to be a male predominance with a 2:1 ratio.

Risk factors for oxalate stones (Calcium oxalate)

- foods high in oxalate, (such as spinach, rhubarb and tea)
 - In patients who have oxalate kidney stones, dietary restrictions are necessary. Foods that should be avoided include: spinach, nuts, chocolate, dry beans, rhubarb and strawberries.
- calcium-restricted diet
- gastrointestinal disease such as Crohn's which increase colonic oxalate absorption
 - in malabsorption, the calcium in the small bowel is bound by the unabsorbed excess fatty acids. Oxalates are left free and are excessively absorbed. Subsequently, they can deposit in the kidney to form stones.
- enteric oxaluria may occur in a number of disorders in which malabsorption results in excessive colonic absorption of oxalate. These include:
 - ⇒ Coeliac disease
 - ⇒ Crohn's disease
 - ⇒ Chronic pancreatitis, and

- **⇒** Short bowel syndrome.
 - Bile salts in the colon increase oxalate absorption.
- Excess vitamin C can be converted to oxalic acid in the body. Subsequent hyperoxaluria can lead to the formation of a kidney stone.

Primary hyperoxaluria

- inherited enzyme deficiency that leads to excessive metabolism of oxalate.
- There are three types:
 - ⇒ types I and III are due to an enzyme defect in the liver glyoxalatepathway
 - ⇒ Type I is the commonest and results in widespread calcium oxalate deposition throughout the body.
 - ⇒ in type II there is failure of reduction of glyoxalate to glycolate.
- Treatment is aimed at increasing urinary pH to make calcium oxalate more soluble. This is by administering supplemental citrate and magnesium.
- Renal insufficiency is common, and patients require a combined liver and kidney transplant in type I disease.

Risk factors for urate stones

- gout
- · ileostomy:
 - ⇒ loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid
- high purine intake,
- High cell turnover. (for example, haematological malignancy).
 - ⇒ Primary polycythaemia would predispose to uric acid stone formation, whereas secondary polycythaemia does not.
- Dehydration
- Thiazide diuretics
 cause hyperuricaemia and can predispose to hyperuricosuria
 and uric acid stone formation.

Stag-horn calculi (Triple phosphate stones: magnesium ammonium phosphate):

- involve the renal pelvis and extend into at least 2 calyces.
- They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate).
- Urea plasma urea lyticum and Proteus infections predispose to their formation
 - ⇒ Proteus produces urease, which leads to hydrolysis of urea to produce ammonia, this leads to precipitation of organic and inorganic salts, one of which is known as struvite, or magnesium ammonium phosphate
- classically produced by urea splitting organisms such as Klebsiella or Proteus.

Drug causes

- drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline
- · topiramate (anti-epileptic) increase the propensity to form calcium phosphate stones.
- thiazides can prevent calcium stones (increase distal tubular calcium resorption)

Renal conditions associated with recurrent urinary tract infections:

- Reflux nephropathy.
- Renal stone (but is less likely than reflux nephropathy)

Hypercalcuria

Thiazide diuretics reduce renal tubular calcium excretion, and therefore can prevent calcium stone formation.

- high urine calcium that is not due to hypercalcemia (idiopathic hypercalciuria)
- Idiopathic hypercalciuria is often familial, the most common cause being increased gastrointestinal absorption of calcium.
- predisposes to stone formation.
- The 24-hour urine is an essential component of the initial evaluation and guides recommendations for prevention
- Treatment including dietary calcium restriction and pharmacological management.
- Both thiazide diuretics and potassium citrate can be used to reduce urinary excretion of calcium. Potassium citrate is generally preferred as it has fewer side effects, and is therefore better tolerated.
- Thiazide diuretics are the drug treatment of choice as they act directly on the renal tubule to reduce urinary calcium excretion (there is a disagreement between onexamination and pastest in which drug is better for hypercalcuria? But after thorough review of sources and uptodate, thiazide is a better choice than potassium citrate)
- Dietary calcium restriction alone has minimal effect on calciuria, given the large amount of calcium that can be mobilised from bone..
- Loop diuretics increase urinary excretion of calcium, and therefore would exacerbate calcium renal stone formation.
- · Pencillamine is used in the management of hypercalcuria associated with Wilson's disease
- Idiopathic hypercalciuria has a familial or sporadic pattern. In the familial pattern an
 autosomal dominant inheritance is present. The type of the disease is identical in affected
 members of the same family and the typical presentation is of recurrent urinary calculi.

Imaging

The table below summarises the appearance of different types of renal stone on x-ray

Туре	Frequency	Radiograph appearance
Calcium oxalate (the most common)	40%	Opaque
Mixed calcium oxalate/phosphate stones	25%	Opaque
Triple phosphate stones	10%	Opaque
Calcium phosphate	10%	Opaque
Urate stones	5-10%	Radio-lucent
Cystine stones	1%	Semi-opaque, 'ground-glass' appearance
Xanthine stones	<1%	Radio-lucent

- patients presenting to the Emergency Department usually have a KUB x-ray (shows 60% of stones)
- the imaging of choice is a non-contrast CT (NCCT). 99% of stones are identifiable on NCCT.

Imaging (European Association of Urology guidelines 2016)

- Ultrasound (US) should be used as the primary diagnostic imaging tool.
 - ⇒ US is safe (no risk of radiation), reproducible and inexpensive.
 - ⇒ US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones.
 - ⇒ the preferred method of imaging in pregnant women.
- KUB (kidney-ureter-bladder radiography) x-ray
 - ⇒ The sensitivity: 44-77% and specificity: 80-87%.
 - ⇒ should not be performed if NCCT is considered.
 - ⇒ KUB is helpful in differentiating between radiolucent and radiopaque stones and be used for comparison during follow-up.
- Non-contrast CT (NCCT) (Non-contrast helical CT kidneys, ureters and bladder (CT KUB))
 - ⇒ The imaging of choice is a non-contrast CT (NCCT).
 - ⇒ become **the standard** for diagnosing acute flank pain
 - ⇒ 99% of stones are identifiable on NCCT.
 - ⇒ Following initial ultrasound assessment, use non-contrast-CT to confirm stone
 - ⇒ more accurate than intravenous urography (IVU), so has replaced it.

· Imaging in pregnant women

- ▶ first-line → ultrasound as the preferred method of imaging
- ➤ second-line → magnetic resonance imaging (MRI)
- ➤ last-line option → low-dose computed tomography (CT)

Management

Acute management of renal colic

Medication

- the British Association of Urological Surgeons (BAUS) recommend diclofenac (intramuscular/oral) as the analgesia of choice for renal colic*
 - ⇒ *Diclofenac use is now less common following the MHRA warnings about cardiovascular risk.
 - ⇒ It is therefore likely the guidelines will change soon to an alternative NSAID such as naproxen
- BAUS also endorse the widespread use of alpha-adrenergic blockers to aid ureteric stone passage
- Stones < 5 mm will usually pass spontaneously.
- Lithotripsy and nephrolithotomy may be for severe cases.

Prevention of renal stones

Calcium stones may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- · high fluid intake
 - ⇒ the main initial treatment
 - ⇒ should aim for a daily urinary output in excess of 2000 ml.
- low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- thiazides diuretics (increase distal tubular calcium resorption) and hence lower calcium concentration in the urine.

Oxalate stones

- · cholestyramine reduces urinary oxalate secretion
- pyridoxine reduces urinary oxalate secretion
- High fluid intake and calcium carbonate are mainstay of prevention.

- Avoid foods high in oxalate such as chocolate, rhubarb and nuts.
- Increasing dietary calcium intake decreases urinary oxalate excretion by reducing absorption (as free oxalate is bound).
- Other treatments which can help enteric hyperoxaluria include:
 - ⇒ Calcium, cholestyramine and magnesium bind strongly to free intestinal oxalate, preventing absorption.
 - ⇒ Iron and aluminium act as intestinal oxalate binding agents.
 - ⇒ Potassium citrate alkalinises the urine, which reduces urinary oxalate excretion.
 - propensity to form stones is reduced when citrate intake is increased.

Uric acid stones

- allopurinol
- urinary alkalinization e.g. oral bicarbonate
- Reducing intake of offal is most helpful at reducing urate excretion

Contraindications to lithotripsy

- absolute contraindication → uncorrected bleeding disorder
- relative contraindications → Ureteric stricture, UTI and cardiac pacemaker

MRCPUK-part-1-September 2008 exam: What is the most likely composition of a staghorn calculus? Struvite

MRCPUK-part-1-September 2012 exam: What are stag-horn calculi normally composed of? Magnesium ammonium phosphate

Cystinuria

- The commonest inborn error of amino acid transport.
- Amino acids excreted in urine are cystine, ornithine, arginine and lysine (mnemonic -COAL).
- The glomerulus is unable to resorb these amino acids, and they are therefore excreted into the urine

Genetics

- autosomal recessive condition.
- The rBAT gene is responsible,
- There are two genes identified:
 - ⇒ SLC3A1 (Chromosome 2)and
 - ⇒ SLC7A9(Chromosome 19)

Features:

- Cystinuria usually presents with recurrent nephrolithiasis in the form of cystine stones (which are often bilateral, multiple, and can form staghorns).
- The renal stones are semi radio-opaque due to the presence of sulphur. (Semi-opaque, 'ground-glass' appearance)
 - ⇒ On plain film, which is not used as much in the UK any more, they are radio-lucent.
 - ⇒ On CT, as with almost all stones, cysteine stones are radio-opaque.

Diagnosis

- Diagnosis of cystinuria can be made by stone analysis; such stones are pale yellow, and analysis reveals high cystine levels. It can then be confirmed by an amino acid chromatogram and quantification of cystine excretion.
- cystine may precipitate out as pathognomonic hexagonally-shaped crystals

Management includes:

- conservative
 - high fluid intake (>4 L/day);
 - alkalinisation
 - ➤ Urine pH should be regularly monitored (aiming for 7.5-8), with sodium bicarbonate being used if necessary (not in hypertensive patients or those with renal failure).
 - ➤ The aim of such treatment is to reduce the urinary cystine concentration to below 300 mg/L.
- If this fails, d-penicillamine, alpha-mercaptopropionylglycine or captopril can be used.
- Cystine stones are not easily broken by lithotripsy, and therefore percutaneous removal is most often used.

Cystinosis

- autosomal recessive
- caused by mutations in the CTNS gene, which encodes a lysosomal transporter of the amino acid cystine. Without this transporter, cystine accumulates in the lysosomes of proximal tubule cells, eventually leading to cell toxicity.
- the most common form of Fanconi syndrome in children.
- · occurs almost exclusively in whites.

Feature

- presents in the first year of life with:
 - failure to thrive, and rickets
 - progressive renal damage (Renal failure develops before the age of 10 years)
 - polyuria, polydipsia
 - Visual impairment (occurs as a result of cystine deposits in the retina and cornea)
 - hypothyroidism

Renal tubular acidosis (RTA)

Recurrent kidney stones, hypokalaemia, acidosis and a normal anion gap is a typical presentation for RTA type 1.

RTA type 2 present with similar biochemical features but is more unlikely to have a history of kidney stones.

Treatment of RTA involves correction of the acidaemia with oral sodium bicarbonate, sodium citrate or potassium citrate

 All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap)

Type 1 RTA (distal) (acid retention)

• Inability to generate acid urine (secrete H+) by a failure of the alpha intercalated cells of the distal tubule to excrete hydrogen ions.

Causes

- Idiopathic, gene defects,
- Autoimmune diseases such as primary biliary cirrhosis, thyroiditis RA, SLE, Sjogren's,
- Drugs: amphotericin B toxicity, analgesic nephropathy,
- hypergammaglobulinaemic states,

Features

- hypokalaemia, (as K⁺ reabsorption is linked to H⁺ excretion).
- acidosis
- > low urinary ammonium production
- inability to lower the urinary pH below 5.3 after ammonium chloride administration despite systemic acidosis
- low urinary citrate
- Hypercalciuria: These predispose to renal stones, rickets or osteomalacia and nephrocalcinosis

Complications

- nephrocalcinosis and renal stones (Alkaline urine increases the risk of calcium deposition)
- Osteomalacia develops because of calcium loss and buffering of retained H+ in bone

Management

Bicarbonate and potassium supplements should be given to maintain adequate plasma levels.



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal) (bicarbonate loss)

Fanconi syndrome (RTA type 2) is associated with Wilson's disease

- · decreased HCO3- reabsorption in proximal tubule
- · very rare in adult practice
- As the distal tubule functions normally, the acidosis is less severe than type 1 RTA, and they urine has a pH of less than 5.3.
- Causes include
 - idiopathic,
 - as part of Fanconi syndrome,
 - Wilson's disease,
 - cvstinosis.
 - lead poisoning
 - > myeloma
 - outdated tetracyclines
 - carbonic anhydrase inhibitors
- Features
 - acidosis, hypokalaemia
 - ▶ hypophosphataemia → increased risk for hypophosphatemic rickets.
- Complications
 - osteomalacia (Phosphate wasting results in marked bone demineralisation)

Type 4 RTA (hyperkalaemic)(hypoaldosteronism)

- · the most common renal tubular disorders
- Causes include:
 - Aldosterone deficiency (hypoaldosteronism): decreased aldosterone production, secondary to:
 - adrenal insufficiency
 - diabetes

- ❖ Diabetic nephropathy → decreased renin production → Hyporeninaemic hypoaldosteronism → low sodium and raised potassium
- Patients with diabetes may have impaired extrarenal potassium homeostasis, caused by a lack of insulin, and autonomic neuropathy with resulting impaired beta2 -mediated influx of potassium into cells.
- chronic reflux nephropathy

Aldosterone resistance

- → 1.Drugs:
 - Non-steroidal anti-inflammatories.
 - angiotensin converting enzyme inhibitors, angiotensin 2 receptor blockers.
 - eplerenone, spironolactone,
 - trimethoprim,
 - pentamidine
 - heparin,
 - cyclosporine
 - → 2.Pseudohypoaldosteronism

Features:

hyperkalaemia

 usually mild but may be exacerbated by drugs such as beta-blockers and ACE inhibitors.

➢ low sodium

- > metabolic acidosis
- Urinary pH is commonly normal
- > reduction in renin and aldosterone leads in turn to a reduction in proximal tubular ammonium excretion

Treatment:

- ⇒ Treatment is usually successful with **conservative measures** such as:
 - stopping provocatory agents,
 - low potassium diet.
- ⇒ Small doses of **fludrocortisone** could be considered for refractory cases.

Type 3 RTA (Juvenile RTA) is combined proximal & distal RTA.

- · autosomal recessive
- · Results from inherited carbonic anhydrase II deficiency.
- 70% of the reported cases are from the Magreb region of North Africa
- rarely discussed
- described as a failure to generate NH3 in the setting of a decreased glomerular filtration rate.

Features:

- > normokalaemic hyperchloraemic metabolic acidosis.
- A syndrome of osteopetrosis
- Renal tubular acidosis
- Cerebral calcification
- Mental retardation.

Туре	Type 1	Type 2	Type 4
Location	Distal tubules	Proximal tubules	Adrenal
Acidosis?	Yes (severe)	Yes	Mild when present
Potassium	Hypokalemia	Hypokalemia	Hyperkalemia
Pathophysiology	H+ secretion	Bicarb reabsorption	hypoaldosteronism/ pseudohypoaldosteronism

January 2010 exam: Which feature is most likely to be seen as a consequence of type 1 renal tubular acidosis?

→ Nephrocalcinosis

Renal vascular disease (RAS)

Flash pulmonary oedema, U&Es worse on ACE inhibitor, asymmetrical kidneys → renal artery stenosis - do MR angiography

The presence of difficult to treat hypertension, renal impairment, evidence of other atherosclerotic disease (carotid bruit) and discrepent renal size makes renovascular disease a distinct possibility.

- Renovascular disease is due to disease affecting the arterial supply of the kidney(s).
- The resulting renal hypoperfusion leads to hyperactivation of the renin-angiotensinaldosterone axis, causing hypertension.
- In one third of cases the disease is bilateral; 40% may have peripheral vascular disease and there may be proteinuria.

Suspicion for renal artery stenosis:

- Current UK guidelines with regard to chronic kidney disease recommend referral for further investigation of atherosclerotic renal artery stenosis when there is:
 - > Refractory hypertension (BP >150/90 mmHg despite 3 antihypertensives);
 - Recurrent episodes of pulmonary oedema despite normal left ventricular function;
 - Rise of >20% serum creatinine or fall of GFR >15% over 12 months with high clinical suspicion of widespread atherosclerosis, or during the first 2 months after initiation with an ACE inhibitor or angiotensin receptor blocker.

A rise in serum creatinine more than 20% above the baseline after starting an (ACEI) → hold the drug, monitor renal function and investigate for renal artery stenosis.

Unilateral renal artery stenosis (RAS) <u>has two common causes:</u>

- 1. Atherosclerosis: usually men over the age of 45 years and typically involves the aortic orifice or the proximal 2 cm of the main renal artery.
- 2. Fibromuscular dysplasia: usually women younger than the age of 50 years and typically involves the middle and distal main renal artery or the intrarenal branches.

Causes

- Atherosclerosis is most common cause (> 95% of patients).
- Arteriosclerosis (renal artery sclerosis) is a more common cause of RAS than fibromuscular dysplasia.
 - ⇒ 40% may have peripheral vascular disease (PVD) with intermittent claudication
 - ⇒ there may be proteinuria.
- In younger patients however, fibromuscular dysplasia (FMD) needs to be considered.
 - > FMD is more common in **young women**
 - > and characteristically has a 'string of beads' appearance on angiography.
 - > Patients respond well to balloon angioplasty
 - > renal artery narrowing is unlikely to progress
- Takayasu's arteritis
- Congenital RAS is extremely rare and may be associated with coarctation of the aorta

Associated risk factors

• Smoking and hypertension that cause atheroma elsewhere in the body.

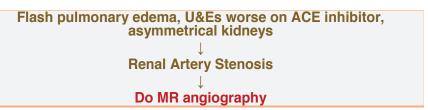
Presentation It may present as:

- Hypertension, which can be resistant to standard treatment.
- · chronic renal failure
- 'flash' pulmonary oedema.
- It can also lead to renal impairment when patients are started on ACE inhibitors or angiotensin-II receptor antagonists, hypokalaemia or flash pulmonary oedema.
 - ACE inhibitor → reduce vasoconstriction in the <u>efferent</u> arterioles, which in turn reduces glomerular filtration pressure. In patients with RAS this can often prompt a precipitous drop in glomerular filtration rate.
 - A rise in creatinine of 15% from baseline is expected with commencement of an ACE-inhibitor.

Investigation

- MR angiography
 - the investigation of choice and can be performed safely in patients with CKD stage 3 and 4
- · CT angiography.
 - Commonly used but can be complicated by radio-contrast nepropathy in patients with CKD.
- conventional renal angiography
 - less commonly performed used nowadays, but may still have a role when planning surgery
- U/S

- Atherosclerotic renal artery stenosis (RAS) is suggested by the asymmetric reduction in renal size on U/S, with mild proteinuria quite common in the condition.
- > Typical ultrasound changes are asymmetrical kidneys; the affected kidney >2 cm smaller than the unaffected kidney.
- ↑↑ Aldosterone
- ↑↑ Renin
 - Serum renin can differentiate renal artery stenosis (↑↑ Renin +↑↑ Aldosterone) from primary hyperaldosteronism (↓↓ Renin +↑↑ Aldosterone)
 - ↑↑ Renin work as a mechanism to improve renal perfusion.
 - ➤ ↓↓ Renin in primary hyperaldosteronism is due to the resulting hypertension causing excessive renal perfusion, which results in decreased renin production (negative feedback mechanism).



Treatment:

- Optimize vascular risk factors,
- cautious use of ACE inhibitors and angiotensin-II receptor antagonists and avoiding other nephrotoxics.
- The current evidence favours medical therapy in these patients, that is, an antiplatelet agent (aspirin), lipid lowering therapy (simvastatin) and tight blood pressure control (amlodipine).
- No benefit of vascular intervention such as stenting.
 - ➤ The ASTRAL trial showed no significant difference between stenting and medical therapy, it is often decided on an individual level.
- Although patients with unilateral renal artery stenosis who have recurrent pulmonary
 oedema may benefit from stenting, the optimal first step is control of hypertension. Per
 se, better targeting of blood pressure is likely to reduce the number of episodes of heart
 failure.
- Renal artery stenting to reduce further risk of pulmonary oedema is the next step
 following medical therapy to control blood pressure. The subsequent reduction in renin
 production will reduce the incidence of heart failure.
- Although surgical renal artery bypass is successful, it is invasive and associated with significant operative morbidity versus percutaneous stent insertion.

Indication for stenting in renal artery stenosis:(mrcpass.com)

- hemodynamically significant renal artery stenosis
 - Flash pulmonary oedema
 - episodic pulmonary edema,
 - congestive cardiac failure,
 - unstable angina.

Prognosis

poor prognosis (80% mortality at five years) is related to concurrent coronary disease.

Lupus nephritis (SLE: renal complications)

Epidemiology

- Lupus nephritis affects a **third of patients** early in the disease
- it is frequently un-recognised until nephritic and/or nephrotic syndrome with renal failure occur.

WHO classification

- · class I: normal kidney
- class II: mesangial glomerulonephritis
- class III: focal (and segmental) proliferative glomerulonephritis
- · class IV: diffuse proliferative glomerulonephritis
- · class V: diffuse membranous glomerulonephritis
- class VI: sclerosing glomerulonephritis
 - > end stage renal disease
 - > irreversible
 - > not respond to any immunosuppression

Class IV (diffuse proliferative glomerulonephritis)

- the most common type in SLE.
- the most severe form, affecting > 50% of glomeruli,
 - carries the worst prognosis for progression to renal failure
- Renal biopsy characteristically shows:
 - > endothelial and mesangial proliferation, 'wire-loop' appearance
 - > the capillary wall may be thickened secondary to immune complex deposition
 - electron microscopy shows subendothelial immune complex deposits
 - granular appearance on immunofluorescence
- Treatment
 - high dose steroids and pulses of intravenous cyclophosphamide (initially given monthly for six months and then quarterly).
 - Pulsed intravenous cyclophosphamide appears to be as effective as oral cyclophosphamide but has lower toxicity.

Class V (Membranous nephropathy in SLE)

- Nephrotic syndrome without haematuria in a patient with (SLE) suggests membranous nephropathy (class V)
- The lesion is differentiated from idiopathic (non-lupus) membranous nephropathy by:
 - The presence of tubulo-reticular structures on electron microscopy, immune deposits along the tubular basement membrane (in addition to the glomerular basement membrane)
 - and the presence of concurrent subendothelial and mesangial immune deposits (in addition to the subepithelial deposits typical of membranous)
 - Class V lupus nephritis is the only form of renal disease in SLE where serological and clinical manifestations of the underlying disease may be absent. Complement levels may be normal and dsDNA antibodies may be absent

Clinical features

- Hypertension is found at presentation in 20-50%
- 20-30% present with acute renal failure
- Lupus nephritis typically occurs in SLE patients with extrarenal symptoms such as a rash, arthralgia, Raynaud's phenomenon, and pleuro-pericarditis

Laboratory features

- Proteinuria is found in all patients with lupus nephritis and in 50-60% of cases is heavy enough to lead to a nephrotic syndrome
- Microscopic haematuria (80% of patients)
- In lupus nephritis a biopsy is indicated in those patients with abnormal urinalysis and/or reduced renal function, for histological classification, disease activity, chronicity and prognosis.

Immunological features

- the pathognomonic feature of lupus on renal biopsy is 'full house' immunology on immunostaining, ie mesangial deposition of IgA, IgG, IgM, C3 and C4
 - This differentiates the necrotising glomerulonephritis with crescent formation seen in lupus from a similar pattern which is seen in systemic vasculitis, as the latter condition is 'pauci immune', ie no immunoglobulin deposition
- Lupus nephritis is associated with activation of the classical pathway, and often associated with suppression of both C3 and C4.

Prognosis

- Features associated with a poorer prognosis, and increased risk of progression to end stage renal failure include:
 - > young age (<23)
 - > Increased serum creatinine
 - > Diffuse proliferative lesions (WHO classification class IV) and
 - high chronicity index on renal histologic analysis.

Management

- treat hypertension
- corticosteroids if clinical evidence of disease
- immunosuppressants e.g. azathiopine/cyclophosphamide
- patients with type IV (and sometimes type III, where < 50% of glomeruli are involved) should be treated with a combination of cyclophosphamide and steroids.

<u>Urinary incontinence (UI)</u>

Epidemiology

- common problem, affect around 4-5% of the population.
- more common in elderly females.

Risk factors

- · advancing age
- · previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification

- urge incontinence /overactive bladder (OAB):
 - due to detrusor over activity
 - > characterized by involuntary loss of urine after sudden desire to urinate.
 - Cystourethroscopy may be performed in patients with urge incontinence to exclude the presence of stones as the primary cause.
 - Urge incontinence may present with frequency, which is defined as urinating more than <u>eight</u> times in the 24 hours.
- stress incontinence: leaking small amounts when coughing or laughing
 - ➤ coughing, sneezing, and laughing → ↑ intra-abdominal pressure and overwhelm the strength of bladder sphincter muscles in those with <u>weak pelvic floors</u>.

- > Outlet incompetence in stress incontinence is due to:
 - urethral hypermobility or
 - intrinsic sphincteric deficiency.
- most common in younger women.
- > There is an increased risk of stress incontinence with pregnancy
- ➤ Obesity → ↑ pressure on pelvic tissues → weakening of pelvic structures.
- mixed incontinence: both urge and stress
- overflow incontinence:
 - causes
 - bladder outlet obstruction, e.g. prostate enlargement
 - Neurogenic bladder (detrusor areflexia)
 - characterized by:
 - absent bladder sensation, decreased tone, increased capacity, hesitancy, and significant residual urine.
 - caused by :
 - → diabetes mellitus.
 - → multiple sclerosis,
 - → cerebrovascular disease (Upper motor neuron lesions) → affect descending pathways from the brain → delayed bladder sensation → urinary retention → overflow incontinence.
 - → Parkinson's disease.
 - → spinal injuries (damage to the conus, cauda equina, and sometimes S2-4 nerve roots)
 - diagnosis
 - Cystometry is the gold standard for the diagnosis
 - increased post-void residual urine on catheterization or ultrasound.
 - Treatment
 - relieve obstruction e.g. catheterization
 - Sacral nerve stimulation can be used for the management of patients with idiopathic detrusor inactivity

Investigation

- bladder diaries should be completed for a minimum of 3 days
- · vaginal examination to exclude cystocele
- urine dipstick and culture
- urodynamic studies

Anticholinergics for urge incontinence are associated with confusion in elderly people - mirabegron is a preferable alternative

antimuscarinics (e.g. Oxybutynin, Tolterodine) the usual treatment for urge incontinence are contraindicated in patients with a history of urinary retention.

Management depends on whether urge or stress UI is the predominant picture.

- If urge incontinence is predominant:
 - bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
 - bladder stabilising drugs: (antimuscarinic) is first-line
 - modern anticholinergics (Solifenacin) are recommended vs traditional agents, such as oxybutynin:

- because oxybutynin is thought to have particularly negative effects on cognitive function in the elderly.
- A meta-analysis has shown that the class as a whole may affect the long-term risk of dementia. As such, dose titration to the minimum level required to control symptoms is recommended.
- Oxybutynin is an effective treatment for detrusor instability and is a parasympathetic muscarinic antagonist.
 - dry mouth is a problem in up to 70% of cases.
 - not recommended for elderly because it is the most negative of the anticholinergic class with respect to its effects on cognitive function.
- In older men, tolterodine is preferred to oxybutynin as the latter has a greater risk of causing confusion.
- If anticholinergics fail or are contraindicated, mirabegron may be trialled.
 - Mirabegron activates the β₃ adrenergic receptor in the detrusor muscle in the bladder, which leads to muscle relaxation and an increase in bladder capacity
- > surgical management: e.g. sacral nerve stimulation
 - indicated if not respond to pharmacological intervention or unable to tolerate it.
- If <u>stress incontinence</u> is predominant:
 - pelvic floor muscle training:
 - NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
 - > surgical procedures: e.g. retropubic mid-urethral tape procedures

Which pharmacotherapies represents the most appropriate initial management step for overactive bladder?

→ Tolterodine

MRCPUK-part-2-March 2017: A 72-year-old woman with urinary incontinence. Urodynamic studies confirm detrusor overactivity and significant post-voiding residual volume. She is unable to tolerate oxybutynin for bladder control due to postural hypotension and GI symptoms. what is the most appropriate intervention for control of her bladder symptoms?

→ Sacral nerve stimulator

MRCPUK-part-2-March 2018: A 74-year-old woman with urge incontinence. Urine dipstick testing and post-void residual bladder volume are normal. Routine urea and electrolytes are also normal. She has attempted bladder training exercises but has not managed to improve her symptoms.

What is the most appropriate next step?

- → Solifenacin
 - modern anticholinergics (Solifenacin) are recommended vs traditional agents, such as oxybutynin, because oxybutynin is thought to have particularly negative effects on cognitive function in the elderly.

Urinary retention

Drug causes

- Amitriptyline has anticholinergic effects being associated with tachycardia, dry mouth and urinary retention.
- ➤ These features are not typical of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or seratonin and noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine with urinary retention and dry mouth rarely reported.
- ➤ Diazepam, a benzodiazepine does not have anticholinergic effects. It has been associated with urinary retention, but this is much less common than with anticholinergics.
- Complication of recovery from obstructive uropathy:
 - Amelioration of urinary obstruction and subsequent recovery initially results in a large electrolyte and water loss. And over the next few days as the tubules recover their function his urine will begin to concentrate appropriately.
 - ➤ The main approach to management in such patients is to ensure they remain adequately hydrated while their kidneys recover their ability to concentrate urine and manage fluid balance.
 - Supplement oral intake with intravenous fluids
 - > The patient should not be fluid restricted as this would lead to severe dehydration.
 - Osmotic cerebral changes precipitated by urinary <u>sodium loss</u>, the major intravascular cation, is the cause of drowsiness.
 - Hypocalcaemia and hypomagnesaemia may occur as tubular reabsorption is suboptimal in the early stages of recovery but is unlikely to affect conscious level.
 - > Acid-base status should improve after relief of the obstruction.

Benign prostatic hypertrophy (BPH)

Risk factors

- Age: around 50% of 50-year-old men will have evidence of BPH and 30% will have symptoms. Around 80% of 80-year-old men have evidence of BPH
- Ethnicity: Black > White > Asian

Features

BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorized into:

- Voiding symptoms (obstructive): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying
- Storage symptoms (irritative) urgency, frequency, urgency incontinence and nocturia
- Post-micturition: dribbling
- Complications: urinary tract infection, retention, obstructive uropathy

Investigations

 If the suspicion is of prostatic hypertrophy, then post-void residual volume is the best way to estimate the degree of bladder obstruction.

Management options

- Watchful waiting
- Medication:

- \triangleright α -blocker (e.g. tamsulosin, alfuzosin) \rightarrow for rapid symptom relief
 - Considered first-line, improve symptoms in around 70% of men
 - α-Blockers relax the smooth muscle of the bladder neck and can improve urinary flow rates
 - smooth muscle tone (prostate and bladder)
 - Adverse effects: dizziness, postural hypotension, dry mouth, depression
- \succ 5 α-reductase inhibitors (e.g. finasteride and dutasteride) \Rightarrow to reduce prostate volume
 - Block the conversion of testosterone to dihydrotestosterone (DHT), which induces BPH
 - Unlike α-1 antagonists causes a reduction in prostate volume and hence may slow disease progression. This however takes time and symptoms may not improve for 6 months.
 - They may also ↓ PSA concentrations by up to 50%
 - Adverse effects: erectile dysfunction, ↓ libido, ejaculation problems, gynecomastia
- The use of combination (α-1 antagonists, 5 α-reductase inhibitors) therapy was supported by the medical therapy of prostatic symptoms (MTOPS) trial
- Surgery: transurethral resection of prostate (TURP)

Medications for BPH

	α_1 -Blockers	5α-REDUCTASE INHIBITORS
Drugs	Prazosin, doxazosin, terazosin, tamsulosin.	Finasteride.
Mechanism	\downarrow contractility of the prostate and bladder neck.	Block testosterone conversion to the more potent dihydrotestosterone.
Results	Improve symptoms and urinary flow rates; more effective than 5α -reductase inhibitors for symptom relief.	Improve symptoms; ↓ prostate size and PSA, especially in men with larger prostates.
Side effects	Orthostatic hypotension, nasal congestion, dizziness, fatigue.	\downarrow libido, ejaculatory dysfunction, impotence.

Prostatic carcinoma

A man of advanced age presenting with bony metastases is most likely to have metastatic prostate cancer.

Overview

- These are adenocarcinomas
- hormonal factors are thought to play a part in the aetiology
- As a rule, prostate cancer is more aggressive in younger men.
- Prostate cancer begins in the outer peripheral zone of the prostate, and grows outward, invading surrounding tissue. BPH begins in an area of the inner prostate called the transition zone, a ring of tissue that makes a natural circle around the urethra. In BPH, the growth is inward toward the prostate's core.

Epidemiology

- Prostate cancer is now the most common cancer in adult males in the UK and is the second most common cause of death due to cancer in men after lung cancer.
- By 80 years of age some 80% of men appear to have malignant foci within the prostate gland
- Prostatic carcinoma is found in 10-30% of patients with BPH.

Risk factors (BPH is not a risk factor)

- † age (the strongest risk)
- obesity
- High intake of animal fats
- low intake of selenium
- Afro-Caribbean ethnicity
- family history: 5-10% of cases have a strong family history

Features

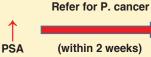
- Localised prostate cancer is often asymptomatic. This is partly because cancers tend to
 develop in the periphery of the prostate and hence don't cause obstructive symptoms early
 on.
- bladder outlet obstruction: hesitancy, urinary retention
- haematuria, haematospermia
- pain: back, perineal or testicular
- digital rectal examination: asymmetrical, hard, nodular enlargement with loss of median sulcus

examination

Investigation (NICE 2015)

- lower urinary tract symptoms or
- erectile dysfunction or
- visible haematuria





- Prostate-specific antigen (PSA)
 - > (PSA) may be elevated in:
 - Prostatitis
 - Benign prostatic hyperplasia, and
 - Prostate cancer.
 - > Some prostatic carcinomas may not be associated with an elevated PSA.
 - > False positives PSA associated with:
 - UTI & catheterisation thus should be measured at least two weeks after a treated UTI.
 - prostatic needle biopsy
 - PR examination
 - False negatives PSA: Finasteride is the only factor likely to decrease the level of serum PSA.
- Trans-rectal prostatic biopsy
 - > The most commonly used pathological grading system is the **Gleason score**
 - ➤ The most well differentiated tumours have a Gleason score of 2, and the most poorly differentiated a Gleason score of 10.
- Bone scan, CT abdomen and pelvis also indicated to assess both extent of bony
 metastases and local spread. (metastases may mimic the appearance of Paget's)

Management: depends on histological grading of the tumour

management: depends on mistological grading of the tamour		
prostate cancer stage	Treatment options	
Localised (T1/T2) T1 - clinically unapparent disease T2 - palpable disease confined to prostate Localised advanced (T3/T4) T3 = beyond prostatic capsule T4 = involves bladder neck or rectum Most men will have occult mets	conservative: active monitoring & watchful waiting radical prostatectomy radiotherapy: external beam and brachytherapy hormonal therapy: see below radical prostatectomy radiotherapy: external beam and brachytherapy	
Metastatic	hormonal therapy • Synthetic GnRH agonist > e.g. Goserelin (Zoladex) and Leuprolide > cover initially with anti-androgen to prevent rise in testosterone • Anti-androgen > such as bicalutamide, or flutamide > cyproterone acetate prevents DHT binding from intracytoplasmic protein complexes Orchidostamy	
	Orchidectomy	

- Synthetic GnRH agonist (Buserelin, Goserelin, leuprolide)
 - Decreased androgen production
 - gonadotrophin releasing hormone agonist that exerts its actions at the level of the pituitary gland.
 - Initially treatment causes increased gonadotrophin release; however, after a few weeks of continued therapy, gonadotrophin production is inhibited, and testosterone levels fall.
 - The initial increase in testosterone levels may be accompanied by a 'flare' in disease symptoms in some patients.
- docetaxel-based chemotherapy
 - indicated only for patients with hormone-refractory cancer.
- Samarium-153 is a radionuclide useful in treating prostate cancer with painful bone metastases and is not useful when the patient is asymptomatic.

What histological grading system is used to grade prostate cancer?

- Gleason grading
 - Gleason grading takes account of the most prevalent tumour pattern in the pathological system (1-5) and the second most prevalent tumour pattern (1-5).
 - It is presented as, for example, Gleason 3+4 = 7. This is important as a Gleason 4+3 = 7 obviously has a worse prognosis than a Gleason 3+4 = 7 even though they both have the same total score.

Renal cell cancer (RCC) (also known as hypernephroma)

Classical triad: haematuria, loin pain, abdominal mass

Overview

- usually arise from the epithelial cells of the proximal convoluted tubule.
- Clear cell RCC is the most common histological variant (~ 80% of all cases).
- Most cases are sporadic, although positive family history increases risk 4-fold.

Epidemiology

- Most common malignancy of the renal parenchyma (85% of renal cancers in adults are RCC)
- Sex: ♂ > ♀ (~ 2:1)
- Age of onset: 60-80 years

Associations

- smoking
- von Hippel-Lindau syndrome (the most likely inherited condition)
 - is an inherited syndrome in which cysts or tumours in the kidney, pancreas, adrenal gland, epididymis, cerebellum, and spinal cord may form.
 - > (30 50% develops renal cell tumors)
- tuberous sclerosis
- incidence of renal cell cancer is only **slightly** increased in patients with autosomal dominant polycystic kidney disease

Features

- · Often asymptomatic and diagnosed incidentally.
- the classical triad of: Haematuria, Loin pain, A palpable mass.
 - only 5–10% of patients present with all three components of the triad
 - ➤ Haematuria is the most common presenting symptom (50-60% of cases)
- Anaemia (common) → Fatigue
- Symptoms of local spread
 - left varicocele (due to occlusion of left testicular vein)
 - ➤ Budd-Chiari syndrome: (due to hepatic vein obstruction → hepatomegaly, ascites, lower limb edema, hepatic dysfunction)
- Paraneoplastic syndromes:
 - ➤ may secrete renin → Hypertension
 - ➤ may secrete erythropoietin (polycythaemia) →Increased plasma viscosity.
 - > may secrete parathyroid hormone (hypercalcaemia).
 - ➤ may secrete ACTH → Secondary hypercortisolism → myopathy
- · Symptoms of metastatic disease
 - 25% have metastases at presentation
 - Commonest sites of metastases are lung (50-60%) and bone (30-40%)
- pyrexia of unknown origin
- Urinalysis may show sterile pyuria

Investigations

- Ultrasound scan of the renal tract
 - > the first investigation of choice,
 - as it is able to pick up 95% of renal cell carcinomas greater than 1 cm in diameter.
 - It would also exclude infective or inflammatory collections within the renal tract.
- CT abdomen/pelvis (contrast-enhanced CT)
 - Definitive test for diagnosis and staging of RCC.
 - If clinical presentation or ultrasound findings are suspicious for RCC, CT imaging is essential.
- MRI abdomen/pelvis
 - Modality of choice for diagnosis and staging in patients where contrast dye is contraindicated (due to renal insufficiency or allergy).

Management

- · for confined disease:
 - > partial or total nephrectomy depending on the tumour size
 - no role for adjuvant therapy after surgery
- for metastatic disease:
 - Targeted molecular therapy
 - receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib)
 - first line therapy
 - have been shown to have superior efficacy compared to interferonalpha
 - recommended by NICE as a treatment for advanced renal cell carcinoma.
 - Sunitinib is superior to interferon alfa in improving progression-free survival. Also, interferon alfa has significant toxicity.

Prognosis

- Prognosis is related to tumour staging:
 - > the 5-year survival rate is around 80-100% in those with TNM stage-1 lesions, but this falls to 5-10% in those with stage-4 lesions
- Risk of distant relapse remains 30% for curatively resected renal cell carcinoma.

Wilms' tumour

- Wilms' nephroblastoma is one of the most common childhood malignancies.
- typically presents in children under 5 years of age, with a median age of 3 years old.
- primarily **composed of blastema**, which is primitive kidney mesenchyme.

Features

- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- hypertension
- · other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)
- Histologic examination is characterized by blastemal, stromal, and epithelial cells (triphasic tumor).

Associations

- Beckwith-Wiedemann syndrome
- as part of WAGR syndrome with Aniridia, Genitourinary malformations, mental Retardation
- hemihypertrophy
- around one-third of cases are associated with a mutation in the WT1 gene on short arm of chromosome 11

Management

- nephrectomy
- chemotherapy
- · radiotherapy if advanced disease

prognosis:

• good, 80% cure rate

Angiomyolipoma

Overview

- the most common benign tumour of the kidney
- is a benign hamartomatous tumor composed of blood vessels, smooth muscle cells and fat cells.
- caused by mutations in either the TSC1 or TSC2 genes, which govern cell growth and proliferation.

Association

- · commonly seen among patients with tuberous sclerosis.
- also commonly found in women with the rare lung disease lymphangioleiomyomatosis.

Presentation:

- retroperitoneal hemorrhage (most frequent)
- · unilateral flank mass.

Diagnosis

- There are three methods of scanning that detect angiomyolipoma: ultrasound, CT and MRI.
- Ultrasound
 - is standard and is particularly sensitive to the fat in angiomyolipoma but less so to the solid components. However it is hard to make accurate measurements with ultrasound
- CT
 - ➢ is very detailed and fast and allows accurate measurement. However, it exposes the patient to radiation and the dangers that a contrast dye used to aid the scanning may itself harm the kidneys.
- MRI
 - ➤ is safer than CT but many patients (particularly those with the learning difficulties or behavioural problems found in tuberous sclerosis) require sedation or general anaesthesia and the scan cannot be performed quickly.
- Biopsy
 - ➤ Some other kidney tumours contain fat, so the presence of fat isn't diagnostic. It can be difficult to distinguish a fat-poor angiomyolipoma from a renal cell carcinoma and a lesion growing at greater than 5 mm per year may warrant a biopsy in order to distinguish it from this form of cancer.

Treatment

- Large angiomyolipoma can be treated with embolisation.
- do not normally require surgery unless there is life-threatening bleeding

Bladder cancer

Use of cyclophosphamide in granulomatosis with polyangiitis is associated with increased risk of bladder cancer (transitional cell carcinoma)

Epidemiology

- In the Western world
 - transitional-cell (TCC) → 93% of bladder cancers
 - ➤ squamous-cell carcinomas (SCCs) → 6%
 - ➤ adenocarcinomas → less than 1%
- male: female ratio 3:1
- women generally have a worse prognosis than men.

At the time of diagnosis around 70% of carcinomas are still localised to the bladder, 20% extend to involve regional lymph nodes and 3% present with distant metastases

Risk factors

- Risk factors for transitional cell carcinoma of the bladder include:
 - Smoking
 - Exposure to aniline dyes in the printing and textile industry
 - ➤ Rubber manufacture →(exposure to nitrosamines (used in the manufacture of some cosmetics, pesticides, and in most rubber products))
 - Cyclophosphamide
- Risk factors for squamous cell carcinoma of the bladder include:
 - Schistosomiasis
 - > Calmette-Gurin (BCG) treatment
 - Smoking

Diagnosis

Cystoscopy is the gold standard for diagnosing bladder cancer.

Treatment

- Treatment of choice for localised tumours is transurethral tumour resection, with the use of intravesical chemotherapy.
- Intra-vesical instilling of BCG has virtually replaced cystectomy in the treatment of bladder carcinoma in situ.

Orthotopic bladder reconstruction for carcinoma of the bladder:

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation.
 - Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common
 - > Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons.
 - Associated electrolyte abnormalities may include hypokalemia, hypocalcaemia, and hypomagnesaemia.
 - > it's usually improves with time and is mild.
 - > treat metabolic acidosis with intravenous fluids and bicarbonate.
 - Intravenous infusion of 1.26% sodium bicarbonate and potassium replacement

Metabolic acidosis associated with bladder reconstruction (e.g. for carcinoma of the bladder).

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild.
- Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient.
- Neobladder formation following radical cystectomy or cystoprostatectomy is becoming
 increasingly more common, and medical staff treating patients with neobladders should
 recognise and treat metabolic acidosis with intravenous fluids and bicarbonate.

Rhabdomyolysis

Collapse + ARF → rhabdomyolysis - treat with IV fluids

Rhabdomyolysis can result from co-prescription of clarithromycin and statins

Overview

 Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have acute renal failure on admission

Pathophysiology

- muscle trauma or necrosis → myoglobin (a muscle protein), which may cause tubular damage or blockage, intense renovascular constriction, and local inflammation → Acute renal failure
- Rhabdomyolysis is strongly suggested by the fact that <u>urinalysis is strongly positive for</u> blood, whereas urine microscopy is negative for red blood cells.
 - The positive urinalysis is caused by **myoglobin**, a muscle protein released during muscle damage; this appears in the urine and can cause acute renal failure.

Causes

- seizure
- collapse/coma (e.g. elderly patients collapses at home, found 8 hours later)
- ecstasy
- Crush injury: electrical injury, compartment syndrome, prolonged limb or tourniquet anaesthesia, extensive surgical dissection and infectious or inflammatory myopathies.
- McArdle's syndrome
- Metabolic myopathy
 - should be suspected when myoglobinuria is recurrent, associated with exercise or fasting and occurring with muscle cramps or weakness
 - Carnitine palmitoyltransferase (CPT) deficiency is the commonest cause of inherited metabolic myopathy resulting in recurrent myoglobinuria
 - The enzyme defect is diagnosed using ischaemic forearm testing and muscle biopsy, which demonstrates abnormal lipid or glycogen deposits
- Drugs:
 - statins (should be stopped in any patient presenting with the syndrome.)
 - Statins are metabolised via the CYP3A4 pathway.
 - Drugs that inhibit its action and lead to excess statin toxicity include macrolide antibiotics such as clarithromycin.
 - It is important to note that atorvastatin (as a more hydrophilic agent) is less metabolised by CYP3A4 and hence the side effects of this combination are less profound.

Features

The biochemical features of rhabdomyolysis are raised creatine kinase, hypocalcaemia (especially early after injury), hyperkalaemia and acute kidney injury.

- acute renal failure with disproportionately raised creatinine
- elevated CK, detectable a few hours after injury and peaks at the 48-h stage
- myoglobinuria, on urine dipstick (shows as haematuria),
 - Urine is dark due to myoglobin.

- Dipstick will be positive for blood (a false positive). On microscopy no red cells are seen although there may be pigmented granular casts.
- Dipstick is the most quickly test for diagnosis
- hypocalcaemia (myoglobin binds calcium)
- elevated phosphate (released from myocytes)
- hyperuricaemia
- hyperkalaemia
- metabolic acidosis in severe cases secondary to raised serum lactic acid levels from the ischaemic muscle fibres.
 - The serum lactate is raised which would suggest an acidotic picture over a normal blood gas picture

Management

- IV fluids to maintain good urine output
- · urinary alkalinization is sometimes used

Loin pain-haematuria syndrome

- characterised by severe, unrelenting loin or flank pain and haematuria with dysmorphic features suggesting a glomerular origin
- A recent report suggested an important psychological component (unexplained somatic symptoms, an adverse psychological event preceding the onset of pain and a history of greater analgesic ingestion)
- One possible explanation for the haematuria in some patients is coexistent thin basement membrane disease.
- It was proposed that bleeding into and obstruction of the renal tubules was responsible for the loin pain
- Management
 - ➢ difficult to treat
 - Dependency on narcotic analgesia is common
 - > Some patients undergo autotransplantation of the affected kidney in an attempt to relieve the pain

Renal tuberculosis

- accounts for 15-20% of extra-pulmonary tuberculosis
- The combination of sterile pyuria, haematuria, dysuria and renal tract calcification is highly suggestive of renal tuberculosis
- Many patients have refractory hypertension, which is renin-mediated and presumably due to segmental renal ischaemia
- Excretion urography is the most helpful diagnostic investigation, may show cavitating lesions in the renal papillary areas, commonly with calcification. There may also be evidence of ureteral obstruction with hydronephrosis

Xantho-granulomatous pyelonephritis (XGP)

Pathogenesis

• It develops as an abnormal macrophage response to infection, particularly in the presence of urinary tract obstruction, and is pathologically related to malacoplakia

Clinical features

- A flank mass is usually palpable, thereby distinguishing it from simple acute pyelonephritis
 or renal abscess, and occasionally mimicking renal cancer
- The disease is almost invariably unilateral
- Patients with XGP often appear chronically ill

• Symptoms include anorexia, fevers, weight loss and flank pain

Diagnosis

- The relatively rapid history, leukocytosis, renal impairment and positive urine culture make XPN much more probable than cancer
- Computed tomography is the investigation of choice to confirm the diagnosis, and it
 will show the replacement of renal parenchyma by rounded, low-density areas surrounded
 by a ring of enhancement; it will also establish the extent of the lesion (which may involve
 surrounding structures)

Prognosis and complications

- The course may extending over months or years
- AA amyloid may develop, resulting in the onset of nephrotic syndrome

Vesico-ureteric reflux

Vesico-ureteric reflux management:

- in childhood: surgical intervention would be beneficial.
- When picked up in adulthood, the mainstay of management would be
 - ⇒ blood pressure control
 - ⇒ Strict glycaemic control (reduce the frequency of recurrent infections and reduce the risk of progression to diabetic nephropathy.)
 - ⇒ prompt treatment of UTI and careful surveillance during pregnancy.
- Vesicoureteric reflux refers to the retrograde flow of urine from the bladder to the upper urinary tract
- It is the most common cause of recurrent urinary tract infections in children.
 - ⇒ It is identified in approximately 40% of patients.
- This may occur due to incompetence of the valve at the vesicoureteric junction
- It is most commonly detected the earliest in newborn girls
- Present with recurrent UTI
- Micturating cystourethrography is the most useful investigation to check for vesicoureteric reflux during voiding in children. It is identified in approximately 40% of patients. (not useful in adult women because by this time the reflux tends to disappear)
- the single most appropriate management for grade-V vesicoureteric reflux in child less than 1 year → Antibiotic prophylaxis

grade	Age(year)	scaring	Initial treatment	Follow up
V	<1	No	Antibiotic prophylaxis	Surgery
V	1-5	No	If unilateral: antibiotic prophylaxis	Surgery
V	1-5	No	If bilateral: surgery	
V	1-5	Yes	Surgery	
V	> 5		Surgery	

Grading of vesicoureteric reflux

grade	Description
I	Reflux into a non-dilated ureter
II	Reflux into the upper collecting system without dilatation
III	Reflux into a dilated ureter and/or blunting of calyceal fornices
IV	Reflux into a grossly dilated ureter
V	Gross dilatation of the ureter, renal pelvis and calyces; calyces show loss of papillary
	impression

Chronic reflux nephropathy (Chronic pyelonephritis)

- Chronic pyelonephritis is also known as 'reflux nephropathy':
- starts in infancy or early childhood,
- predisposes to recurrent infections and progressive renal fibrosis and loss of function
- · the kidneys are small, shrunken and scarred

Renal scarring

- is a serious complication of chronic pyelonephritis that occurs due to vesicoureteric reflux.
- It is mediated by cytokines, chemokines and their receptors, complement, adhesion molecules and extracellular matrix proteins.
- The cytokines which seem to play the largest role are:
 - ⇒ interleukin (IL)-1beta,
 - □ IL-3
 - ⇒ Transforming growth factor (TGF)-beta.
 - TGF-beta in particular seems to be pro-fibrotic by recruiting fibroblasts,
 - In a genotype where its production is limited has been shown to be less likely to develop renal scarring.
- Chronic reflux nephropathy should be suspected in the presence of multiple urinary tract infections, including during childhood
- may present with difficult-to-treat hypertension in young age
- The investigation of choice is excretion urography (Micturating cystourethrogram), which may show:
 - an irregular renal outline,
 - calyceal clubbing
 - and cortical scarring on the affected side
- The best course of action is to recognise this condition in childhood and consider surgical
 management where demonstrable ureteric reflux exists, or early intervention with antibiotics
 where repeat infection exists
- Chronic reflux nephropathy is a relatively common cause of end-stage renal failure in late childhood or early adult life if it goes unrecognized

Recommendations for the diagnostic evaluation of uncomplicated pyelonephritis

- Perform urinalysis (e.g. using a dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.
- Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.
- Perform ultrasound of the upper urinary tract to exclude obstructive pyelonephritis.
- Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.

(European association of urology)

Phimosis

- Phimosis is common in 2-year olds
- Prognosis and management
 - Most will slowly dilate, thus Wait and watch is the most appropriate treatment
 - ➤ In those who have persistent problems into teenage years, around 85% will respond to topical steroids, reducing the need for circumcision
 - > Where there is obvious infection, a dorsal slit may be considered

Urethral syndrome

- The condition is common in elderly postmenopausal women due to dryness and atrophy of the urethral tissue
- Presented with dysuria, increased frequency of micturition and sterile urine.
- Treatment: Topical oestrogen cream often results in a dramatic response

Urinary tract infection (UTI) in adults

Causes of UTI:

- Escherichia coli is the first most common
- Staphylococcus saprophyticus is the second most common cause of UTI in sexually active women

Classification of UTI (European association of urology guidelines)		
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant, pre-menopausal women with no known anatomical and functional abnormalities within the urinary tract or comorbidities.	
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters , renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes .	
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.	
Catheter- associated UTIs	UTIs in a person currently catheterised or has been catheterised within the past 48 hours .	
Urosepsis	A systemic, deleterious host response to infection originating from the urinary tract and/or male genital organs. Urosepsis is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia.	

Features

- classic symptoms of (UTI):dysuria, frequency of urination, suprapubic tenderness, urgency, polyuria, haematuria
- upper urinary tract infection (UUTI): evidence of UTI with symptoms suggestive of
 pyelonephritis (loin pain, flank tenderness, fever, rigors or other manifestations of systemic
 inflammatory response).
- **lower urinary tract infection (LUTI):** evidence of UTI with symptoms suggestive of cystitis (dysuria or frequency without fever, chills or back pain).

Diagnosis

- Diagnosis of UTI is primarily based on symptoms and signs. Bacteriuria or pyuria do not establish the diagnosis of UTI.
- The gold standard test for diagnosis of bacteriuria is culture of bladder urine obtained by needle aspiration of the bladder as it minimises the risk of contamination of the urine specimen.
 - > All other techniques (urethral catheter and midstream specimens of urine) carry a higher risk of contamination and therefore produce some false positive results
- Nitrite test:
 - Gram negative organisms test positive on the nitrite test as they convert nitrates to nitrites for energy.
 - Gram positive organisms are unable to reduce nitrate to nitrite and therefore, test negative.
- UTI is usually diagnosed by a bacterial count of >100 000/ml at mid-stream urine (MSU)
- Presentation with a first urinary tract infection associated with haematuria in elderly patient → Re-testing of urine with cytological examination after antibiotics
- Sterile pyuria and negative urine cultures suggest urinary tract infection by the bacteria Neisseria gonorrhoeae or Chlamydia trachomatis.
- Persistent haematuria should be investigated with excretion urography and cystoscopy

If the mid-stream urine (MSU) reveals bacteriuria, in asymptomatic pregnant lady. what is the most appropriate intervention?

- → Repeat sample
 - NICE guidelines recommend a second confirmatory sample to be sent before initiating treatment.

Recommendations for the diagnostic evaluation of uncomplicated cystitis (European association of urology)

Diagnose uncomplicated cystitis based on:

- a focused history of lower urinary tract symptoms (dysuria, frequency and urgency);
- the absence of vaginal discharge or irritation, in women who have no other risk factors for complicated urinary tract infections.

Use urine dipstick testing, as an alternative to culture for diagnosis of acute uncomplicated cystitis.

Urine cultures should be done in the following situations:

- suspected acute pyelonephritis;
- symptoms that do not resolve or recur within two-four weeks after the completion of treatment;
- women who present with atypical symptoms;
- pregnant women.

Management (Sign.uk recommendations for UTI 2012)

- Men
 - ⇒ urine sample should be taken for culture.
 - ⇒ empirical antibiotics with a quinolone in men with symptoms suggestive of prostatitis.
- Non-pregnant women
 - ⇒ LUTI
 - Symptomatic bacteriuria → three-day course of trimethoprim or nitrofurantoin.

- Amoxicillin, ampicillin, nitrofurantoin and oral cephalosporins may be considered as alternatives
- Routine urine culture is not required to manage
- If not respond to trimethoprim or nitrofurantoin → urine for culture to guide change of antibiotic
- asymptomatic bacteriuria → Do not treat with an antibiotic.
- Recurrent UTI → consider using cranberry products to reduce the frequency of recurrence.

⇒ UUTI

- ciprofloxacin (7 days) or co-amoxiclav (14 days).
- Acute pyelonephritis
 - hospital admission should be considered
 - the BNF currently recommends a broad-spectrum cephalosporin or a quinolone (for non-pregnant women) for 10-14 days

• Pregnant women:

- ⇒ Treat symptomatic and asymptomatic UTI
- ⇒ Urine culture before starting empiric antibiotic and 7 days after completion empiric antibiotic treatment.
- ⇒ First line agent → Nitrofurantoin
 - A dose of 50 mg QDS or 100 mg BD of modified release for 7 days is recommended.
 - Care for nitrofurantoin
 - elderly patients may be at increased risk of toxicity.
 - contraindicated in significant renal impairment. The BNF advises against its use in patients with GFR<60.
 - Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate).
- ⇒ Second line →Trimethoprim
 - contra indicated in established folate deficiency, low dietary folate intake, or women taking other folate antagonists.
- ⇒ Third line →cephalosporins
 - There is 20% cross-over with respect to allergy to penicillin and cephalosporins.
- - asymptomatic bacteriuria is associated with premature delivery and low birthweight.
 - routine screening for asymptomatic bacteriuria at antenatal appointments is therefore recommended.
 - Infections in pregnancy should be treated, as 25% of patients will develop acute pyelonephritis

UTI in diabetes

- Data from the American Diabetes Association have shown that 9.4% of people diagnosed with type 2 diabetes had a UTI compared to only 5.7% of those without.
- The most common pathogens isolated from the urine of diabetic patients with UTI were *E. coli* and other Enterobacteriaceae such as *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and Enterococci.
- ➤ Infection with Extended spectrum beta-lactamase-producing *coli* (ESBL-producing *E. coli*) is an increasingly recognised cause of infection in diabetes patients and is associated with poor outcomes.
 - Carbapenems are generally considered the drug of choice for the treatment of ESBL/E. coli (ESBL-EC) infections
 - With a half-life of 4 h, ertapenem is commonly used as it is administered only once daily.
 - Fosfomycin is an oral antibiotic agent that has broad activity against multidrug-resistant pathogen, including ESBL–EC.
 - Another oral antimicrobial agent that can be considered for the treatment of ESBL-EC cystitis is nitrofurantoin.

Extended spectrum beta lactamase (ESBL) urine infection → Intravenous meropenem

What is the next step in management of first episode of UTI in elderly after treatment with antibiotics?

- → Re-testing of urine with cytological examination after antibiotics
 - UTI may develop in patients with an underlying urothelial tumour.
 - Persistent haematuria should be investigated with excretion urography and cystoscopy.
 - Bladder tumours are around 50 times more common than tumours of the ureter or renal pelvis.

Antibiotic guidelines for urinary tract:

The following is based on current BNF guidelines:

Condition	Recommended treatment
Lower urinary tract infection	Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin
Acute pyelonephritis	Broad-spectrum cephalosporin or quinolone
Acute prostatitis	Quinolone or trimethoprim

Asymtomatic bacteriuria (ABU)

Risk factors for asymptomatic bacteriuria

Female sexAge

Sexual activity
 Institutionalisation

Comorbid diabetes
 Presence of catheter

Recommendations for the management of ABU (European association of urology)

- Do not screen or treat asymtomatic bacteriuria in the following conditions:
- women without risk factors:
- patients with well-regulated diabetes mellitus;
- post-menopausal women;
- elderly institutionalised patients;
- patients with dysfunctional and/or reconstructed lower urinary tracts;
- · patients with catheters in the urinary tract;
- patients with renal transplants;
- · patients prior to arthoplasty surgeries;
- patients with recurrent urinary tract infections.
- Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.
- Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.
- Take a urine culture following treatment of asymptomatic bacteriuria to secure treatment effect

UTI in childhood

- In up to 75% cases of single infection, no abnormality can be found
- Escherichia coli is the most common organism isolated (> 70% of cases)
- Chronic diarrhoea or even acute diarrhoea can be a presenting feature of childhood urinary tract infection
- Trimethoprim is often the best initial antibiotic of choice
- In children (particularly neonates and infants), UTI can be haematogenous and may be part of a septicaemic process, therefore, blood cultures and iv antibiotics are necessary

Recurrent urinary tract infection (rUTI)

Definition

two episodes of infection in six months, or three episodes in one year

Recurrent bacteriuria:

- Relapse
 - > diagnosed by the recurrence of bacteriuria with the same organism <u>within 7 days</u> of completing antibacterial treatment and implies <u>failure to eradicate infection</u>.
 - > usually occurs in conditions in which it is difficult to eradicate the bacteria, such as:
 - renal stones.
 - scarred kidneys,
 - polycystic disease or
 - bacterial prostatitis.
- Reinfection
 - occurs when bacteriuria is absent after treatment for at least 14 days, usually longer, followed by recurrence of infection with the same or a different organism.

Incidence

 annual incidence of a single UTI is 30 per 1000 women, with 44% experiencing recurrence within 12 months

Risk factor

Age-related risk factors for rUTI in women

Young and pre-menopausal women	Post-menopausal and elderly women
 Sexual intercourse Use of spermicide A new sexual partner A mother with a history of UTI History of UTI during childhood Blood group antigen secretory status 	History of UTI before menopause Urinary incontinence Atrophic vaginitis due to oestrogen deficiency Cystocoele Increased post-void urine volume Blood group antigen secretory status Urine catheterisation and functional status deterioration in elderly institutionalised women

- · Sexual activity in young females
 - Recurrent cystitis may often accompany the onset of sexual activity in young females
 - The appropriate first-line management is to advise strict attention to personal hygiene, and an increase in fluid intake and subsequent urine flow around times of sexual activity
- Vesicoureteric reflux
- · Chronic reflux nephropathy:
 - \succ the best diagnostic investigation is \rightarrow Micturating cystourethrogram
- Posterior urethral valves
 - > the chief complaint of children with this disorder is a poor urinary stream
- Urinary tract obstruction in BPH:
 - post-void residual volume is the best way to estimate the degree of bladder obstruction

Diagnosis of rUTI

- · should be confirmed by urine culture.
- Do not perform an extensive routine workup in women with recurrent UTI without risk factors. (European association of urology)

Treatment

 After treating the acute infection, <u>low dose antibiotics for 6-12 months</u> are the most evidence based <u>preventive measure</u> for recurrent (UTI) in women and are recommended by Scottish Intercollegiate Guidelines Network and the European Association of Urology guidelines as the standard of care.

Prevention (European association of urology)

- Non-antimicrobial interventions
 - behavioural modifications
 - vaginal oestrogen replacement in post-menopausal women
 - Immunoactive Prophylaxis (in all age groups)
 - bacterial extracts to stimulate the host's immune system to produce antibodies
 - e.g. Oral immunostimulant OM-89
- · Antimicrobial prophylaxis (continuous or post-coital)
 - When non-antimicrobial interventions have failed, continuous or post-coital antimicrobial prophylaxis should be used.
 - For patients with good compliance, self-administrated short-term antimicrobial therapy should be considered.

Catheter-Associated UTI

Overview

- Once catheter is in place, the
- risk of bacteriuria Once catheter is in place:
 - > short-term catheterization (ie, 2-4 days) → 10% 30%
 - ➤ long-term catheterization → 90% -100%
- the most common source of gram-negative bacteremia in hospitalized patients

Causes

- Enteric pathogens (eq. Escherichia coli) are most commonly responsible
- Proteus and Pseudomonas species are the organisms most commonly associated with biofilm growth on catheters.
- Candida, especially Candida albicans, is the second-most-common organism that can cause catheter-associated urinary tract infection or asymptomatic colonization

Diagnosis

 diagnosis of catheter-associated urinary tract infection can be made when the urine culture shows 100 or more CFU per mL of urine from a catheterized patient.

Treatment

- Symptomatic bacteriuria
 - > mild to moderate infections: oral quinolones, usually for 10 to 14 days.
 - > The recommended duration of therapy for severe infections is 14 to 21 days.
- Asymptomatic bacteriuria
 - not recommended, with the following exceptions:
 - patients who are immunosuppressed after organ transplantation,
 - patients at risk for bacterial endocarditis and
 - patients who are about to undergo urinary tract instrumentation

Urinary tract obstruction in children (posterior urethral valves)

Overview

- A poor urinary stream suggests a urinary tract obstruction (usually infravesical)
- . The most common cause in a male child is posterior urethral valves
- posterior urethral valves: symmetrical folds of urothelium extending distally from the prostatic urethra to the external urinary sphincter
- Renal dysplasia is usually associated with posterior urethral valves

Diagnosis

- The best diagnostic method is a micturating cystourethrography
- The other option is endoscopy .

Complications

- 30% of patients experience end-stage renal disease
- Vesicoureteric reflux occurs in half the patients



Third edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Haematology & Oncology

Updated 2022

Haematological changes during pregnancy

- Platelet
 - Isolated thrombocytopenia
 - occur in 8%
 - Usually mild with platelet above 70
 - Occur due to presence IgG antibodies, which are reactive to platelet
 - No intervention recover after delivery
- Hypercoagulable state
 - → ↑ clotting factors
 - result of venous stasis secondary to uterine pressure on great veins of lower extremity
- Anemia
 - → ↑ plasma volume by 50%
 - ➤ RBC mass only ↑ by 30%
 - Result is a dilutional gap of 15-20%
- Leukocytosis
 - result of granulocyte demargination
 - no absolute increase in WBC number

Hyposplenism

Causes

- splenectomy
- sickle-cell
- · coeliac disease, dermatitis herpetiformis
- Graves' disease
- · systemic lupus erythematosus
- amyloid

Features

- Howell-Jolly bodies
- siderocytes

Eosinophilia

Causes

- Pulmonary causes
 - asthma
 - allergic bronchopulmonary aspergillosis
 - > Churg-Strauss syndrome
 - > Loffler's syndrome
 - > tropical pulmonary eosinophilia
 - > eosinophilic pneumonia
 - > hypereosinophilic syndrome
- Infective causes
 - schistosomiasis
 - > nematodes: Toxocara, Ascaris, Strongyloides
 - > cestodes: Echinococcus
- Other causes
 - > drugs: sulfasalazine, nitrofurantoin
 - psoriasis/eczema
 - eosinophilic leukaemia (very rare)

Eosinopenia (Decrease eosinophils)

Causes

- · Cushing syndrome would result in a decrease in eosinophils.
- Corticosteroids can cause eosinopenia through sequestration of eosinophils in lymph nodes.

Hyper-eosinophilic syndrome (HES)

Definition

- peripheral blood eosinophil count of >1.5 for more than 6 months.
- In hypereosinophilic syndrome, the eosinophils represent more than <u>20</u> percent of the cell population in the bone marrow.
- HES are defined as the association of Hypereosinophilia (as defined above), with eosinophil-mediated organ damage, in which other causes for the damage have been excluded.

Features

- Hypereosinophilic syndrome most commonly causes manifestations involving the skin.
- pruritus.
- · fatigue, myalgia,
- · fever, night sweats,
- diarrhoea
- The most common neurological manifestation of hypereosinophilic syndrome is stroke.
- Other symptoms depend on the organ involved:
 - cardiac disease causes chest pain and dyspnoea,
 - respiratory disease presents with a dry cough.

Treatment

- The first line of treatment of patients with non-myeloid hypereosinophilic syndrome is <u>glucocorticoids</u>.
- The best initial therapy for patients with hypereosinophilic syndrome associated with Fip1-like1-platelet-derived growth factor receptor alpha mutation is imatinib.

Lymphopenia

Causes

- common finding in elderly patients.
 - ➤ If greater than 0.5 * 10⁹/l no action is normally needed
- immunosuppressive drugs e.g. methotrexate
- · viral infections e.g. HIV
- non-viral infections e.g. tuberculosis, malaria
- · autoimmune disorders e.g. rheumatoid
- lymphoproliferative disorders

Abnormality	Associated condition(s)	Appearance
Target cells	Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease	
'Tear-drop' (Dacrocyte) poikilocytes	Myelofibrosis (The morphology results because RBCs are mechanically squeezed out of the bone marrow.)	
Spherocytes	Hereditary spherocytosis Autoimmune hemolytic anaemia	
Basophilic stippling	Lead poisoning Thalassaemia Sideroblastic anemia Myelodysplasia	

Abnormality	Associated condition(s)	Appearance
Howell-Jolly bodies	Hyposplenism (Howell-Jolly bodies are the basophilic remnants of the RBC nucleus.)	
Heinz bodies	G6PD deficiency Alpha-thalassaemia	
Schistocytes ('helmet cells')	Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation	
'Pencil' poikilocytes	Iron defiency anaemia	

Abnormality	Associated condition(s)	Appearance
Burr cells (echinocytes) Pyruvate kinase deficiency liver disease		2000
Acanthocytes	Abetalipoproteinemia	(irregularly distributed spicule in red blood cells).
Bite cell (Degmacyte)	G6PD (when spleen removes heinz bodies from RBCs)	

Blood films: typical pictures

Hyposplenism e.g. post-splenectomy

- target cells
- Howell-Jolly bodies
 - > These are spherical bluish inclusions within erythrocytes
 - > They are nuclear fragments of condensed DNA which are normally removed by the spleen.
 - They are seen in severe haemolytic anaemias or in hyposplenic/asplenic patients.
- · Pappenheimer bodies
- siderotic granules
- acanthocytes

Iron-deficiency anaemia

- target cells
- 'pencil' poikilocytes

 if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Myelofibrosis

· 'tear-drop' poikilocytes

Intravascular haemolysis

schistocytes

Megaloblastic anaemia

hypersegmented neutrophils

Congenital Pelger-Huet anomaly

- is a laminopathy associated with mutations in the lamin B receptor.
- This leads to bilobed nuclei in neutrophils and in homozygotes,
- can also be associated with:
 - > skeletal abnormalities which include shortened limbs.
 - Like this patient, heterozygotes usually suffer no symptoms and the neutrophil anomaly is picked up as an incidental finding.

MRCP part-1 - jan 2017

A 23-year-old man with tiredness and was noted to have a **neutrophil abnormality** on his blood film with **bilobed nuclei**. His father has a skeletal anomaly with a short right arm, Examination reveals no lymphadenopathy, and abdominal examination is entirely normal. What is the most likely diagnosis?

→ Congenital Pelger-Huet anomaly

Leucocyte alkaline phosphatase

Raised in	Low in
 myelofibrosis leukaemoid reactions polycythaemia rubra vera infections steroids, Cushing's syndrome pregnancy, oral contraceptive pill 	 chronic myeloid leukaemia pernicious anaemia paroxysmal nocturnal haemoglobinuria infectious mononucleosis

Leukaemoid reaction

Definition

 Presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood.

Mechanism

- This may be due to:
 - > infiltration of the bone marrow causing the immature cells to be 'pushed out' or
 - > sudden demand for new cells

Causes

- · severe infection
- severe haemolysis
- · massive haemorrhage
- · metastatic cancer with bone marrow infiltration

Differentiating chronic myeloid leukaemia from a leukaemoid reaction:

Chronic myeloid leukaemia	Leukaemoid reaction
low leucocyte alkaline phosphatase score	 high leucocyte alkaline phosphatase score toxic granulation (Dohle bodies) in the white cells 'left shift' of neutrophils i.e. three or less segments of the nucleus

Coagulation study

Prothrombin time (PT)

- Prothrombin time (PT) is a measure of the time it takes for the extrinsic pathway to create a fibrin clot.
- tests function of factors (I, II, V, VII, X)
 - defect in any of these → ↑ PT
 - e.g. vitamin K deficiency
- best test to follow warfarin therapy
 - normalized as an INR (international normalized ratio)
 - > note also increases PTT time
- also used to measure hepatic function as most of the factors are synthesized in the liver Used to monitor the extrinsic pathway
- Factors make up the extrinsic pathway:
 - ➤ Damaged endothelium → tissue factor release → Factor VII activation → common pathway activation
- In patients with vitamin K deficiency, the PT is typically prolonged while the partial thromboplastin time (PTT) is usually normal.
- Long-term use of antibiotics → changes in the gut flora → vitamin K deficiency →
 ↑PT
 - Long-term use of antibiotics (particularly cephalosporins like cefepime) would cause changes in the gut flora that result in vitamin K deficiency (due to decreased populations of the bacteria that synthesize it).
 - vitamin K deficiency would impair the gamma-carboxylation of factors II, VII, IX, and proteins C and S.
 - As a result, the **PT**, which **measures the clotting time of the extrinsic pathway** (starting with tissue factor and factor VII), would **increase**, just as it would in a patient on warfarin.

Partial Thromboplastin Time (PTT) (sometimes also called Activated Partial Thromboplastin Time)

- tests function of all factors EXCEPT (VII, XIII)
 - defect in any of these→ ↑ PTT
- when prolonged indicating hemophilia or (sometimes) von Willebrand's Disease.
- best test to follow heparin therapy
 - note also increases PT time
- Used to monitor the intrinsic pathway
- Factors make up the intrinsic pathway:
 - Factors XII, XI, IX, VIII.
- elevated APTT could be due to:
 - treatment with heparin
 - haemophilia
 - > von Willebrand's disease, or
 - antiphospholipid syndrome.

The commonest cause of reduced APTT is → in-vitro clotting cascade activation, but tests should be repeated to exclude pathological causes of hypercoagulability.

DIC vs TTP

- DIC is distinguished from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) based on coagulation studies.
- Although TTP and HUS are also microangiopathic hemolytic anemias, patients with these conditions do not have derangement or consumption of clotting factors.
 - ▶ DIC → Increased PT, PTT, decreased platelets
 - ➤ TTP & HUS → normal PT, normal PTT, and decreased platelets.

Isolated factor deficiency

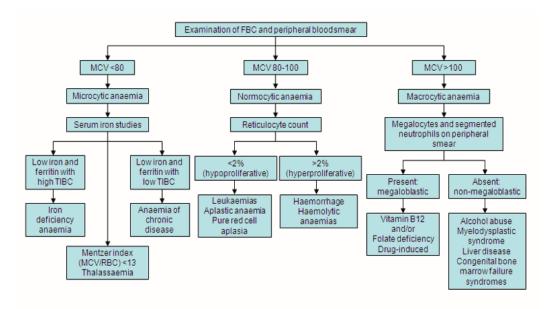
- Normal PT, increased PTT, and normal platelets suggests an isolated factor deficiency such as hemophilia A and B, in which there is a deficiency of factors VIII and IX, respectively.
- An isolated elevated PTT may also suggest von Willebrand's disease.

Disease	PT	PTT	Platelet count	Bleeding time
Warfarin (or vitamin K deficiency)	Raised	Raised (in severe or prolonged cases)/nl	Raised	nl
DIC	Raised	Raised	Decreased	Raised
Thrombocytopenia	nl	nl	Decreased	Raised
Bernard-Soulier	nl	nl	Decreased	Raised
Hemophilia (A or B)	nl	Raised	nl	nl
von Willebrand	nl	nl/raised	nl	Raised
Glanzmann's	nl	nl	nl	Raised

Giant platelet syndrome (Bernard-Soulier syndrome; BSS)

- is a defect in platelet adhesion.
- The genetic defect is in glycoprotein 1b (GP1b).
- characterized by increased megakaryocytes and abnormally large platelets on peripheral smear, hence its name.
- thrombocytopenia and an elevated bleeding time but a normal prothrombin time (PT) and partial thromboplastin time (PTT).
- BSS can be distinguished from a deficiency in von Willebrand factor (vWF) by a ristocetin test.
 - Ristocetin is an antibiotic that causes vWF to bind to GP1b, causing agglutination in normal blood.
 - In patients with either defective vWF or GP1b (BSS), platelets do not aggregate in the presence of ristocetin.
 - The addition of normal plasma corrects this defect in von Willebrand's disease, but not in BSS (because the platelet receptor remains defective).

Assessment of anaemia



From BMJ best practice Causes of normocytic anaemia:

- · anaemia of chronic disease
- · chronic kidney disease
- · aplastic anaemia
- haemolytic anaemia

Causes of macrocytic anaemia:

 can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Normoblastic causes
vitamin B12 deficiencyfolate deficiency	 alcohol liver disease hypothyroidism pregnancy reticulocytosis myelodysplasia drugs: cytotoxics

Causes of microcytic anaemia:

- · iron-deficiency anaemia
- thalassaemia*
 - *in beta-thalassaemia minor the microcytosis is often disproportionate to the anaemia

- A question sometimes seen in exams gives a history of a <u>normal haemoglobin</u> <u>level associated with a microcytosis</u>. <u>In patients not at risk of thalassaemia</u>, this should raise the possibility of <u>polycythaemia rubra vera</u> which may <u>cause an</u> iron-deficiency secondary to bleeding.
- congenital sideroblastic anaemia
- anaemia of chronic disease (more commonly a normocytic, normochromic picture)
- lead poisoning

Iron metabolism

Absorption:

- Upper small intestine.
- About 10% of dietary iron absorbed.
- Fe2+ (ferrous iron) much better absorbed than Fe3+ (ferric iron).
- Absorption is regulated according to body's need.
- Increased by vitamin C (ascorbic acid) and gastric acid.
 - > vitamin C aids iron absorption by reducing iron from the ferric to the ferrous form, and by chelating it into a complex which enhances absorption.
- Decreased by PPIs, tetracycline, gastric achlorhydia, tannin (in tea).
- From an intake of approximately 6 mg/1000 kcal of dietary iron only 15% is bioavailable.

Oral iron absorption.

A. Effectors of iron absorption.		
Inhibiting iron absorption	Facilitating iron absorption	
 Coffee, tea, milk, cereals, dietary fiber, phosphate-containing carbonated beverages Multivitamin or dietary supplements containing calcium, zinc, manganese or copper Antacids, H2 blockers and proton pump inhibitors. Quinolones and tetracycline antibiotics 	 Vitamin C Acidic foods e.g. tomato sauce Non enteric coated iron tablets Fasting ingestion of iron supplements 	
B. Oral iron absorption test.		
Step 1: Measure morning serum iron level (fasting).		
Step 2: Ingest approximately 60mg elemental iron (324 mg ferrous sulphate) with water.		
Step 3: After 1-2 hours, measure the serum iron level.		
Step 4: Compare the serum iron levels.		
Interpretation: An increase in serum iron of >100 $\mu g/dL$ suggests gut absorption is generally adequate.		

Distribution in body

- Total body iron = 4g (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle).
- Haemoglobin = 70%
- Ferritin and hemosiderin = 25%
- Myoglobin = 4%
- Plasma iron = 0.1%

Approximately 4 mg of iron circulate within the plasma. So approximately 0.1% of body iron circulates in the plasma.

Transport

• Carried in plasma as Fe3+ bound to transferrin.

Storage

- Stored as ferritin in tissues.
 - > It is the plasma protein responsible for binding iron,
 - > is an acute phase reactant protein which is increased in inflammatory conditions.

Excretion

 The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut.

Transferrin

- serum transferrin is the bus that carry absorbed iron to storage places & stored as ferritin.
- transferrin saturation is the % of people [iron] carried by that bus [transferrin].
- TIBC is the no. of empty chairs in that bus.
- Transferrin is a glycoprotein responsible for internal iron exchange
 - > Iron (Fe 3+) is carried in the blood bound to transferrin.
 - Fe2+ (ferrous iron) is oxidised to Fe3+ (ferric iron) by caeruloplasmin to bind to transferrin
- Transferrin is the binding protein of iron. So when the levels of ferritin are low, the body signals the liver to synthesize more of Transferrin to maintain the levels of iron
- Pregnancy and oral contraceptive pill (OCP) both increase transferrin.
- Transferrin saturation %
 - > The transferrin saturation % (plasma iron /TIBC x 100) is used as a measure of iron stores.
 - In absence of anaemia, transferrin is about 33% saturated with iron (about one third saturated with iron).
 - > A value below 16% is indicative of iron deficiency.
- iron deficiency → low serum Fe, rise TIBC, rise the transferrin level.
- iron overload → fall in both TIBC and transferrin
- haemochromatosis → increased in Transferrin saturation%
 - the content within mucosal cells is naturally high in haemochromatosis with high iron store saturation.
 - in haemochromatosis TIBC is low because transferrin is FULL of iron and no more empty space, hence LOW TIBC and for the same reason transferrin saturation is high [FULL]

Iron studies

- Serum iron
- Total iron binding capacity (TIBC)
- Transferrin
 - raised in iron deficiency anaemia (IDA)
 - raised in pregnancy and by oestrogen
- Transferrin saturation
 - calculated by serum iron / TIBC
- Ferritin
 - > raised in inflammatory disorders
 - ➢ low in IDA
- Rarer tests
 - ➤ transferrin receptors → increased in IDA
- Anaemia of chronic disease

- > normochromic/hypochromic, normocytic anaemia
- reduced serum and TIBC
- normal or raised ferritin

Iron deficiency anaemia (IDA)

• iron deficiency is the most common cause of anemia worldwide.

Causes

- the commonest cause of iron-deficiency anaemia worldwide being hookworm infection (Necator americanus and Ancylostoma duodenale), which affects 25% of the global population.
- microcytic anaemia in a female should raise the possibility of either gastrointestinal blood loss or menorrhagia.

Features

- Koilonychia (spoon-shaped nails)
- atrophic glossitis
- · post-cricoid webs
 - Plummer-Vinson syndrome (dysphagia, esophageal webs and iron deficiency)
- other cutaneous manifestations of iron deficiency include:
 - > pruritus,
 - dry and brittle hair
 - the hair, skin, nail and mucous membrane changes are often visible before the patient is clinically anemic.
- angular stomatitis

Investigations

- Blood film
 - target cells
 - 'pencil' poikilocytes
 - if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells
- Serum ferritin
 - > Hypoferritinaemia confirms IDA and is the preferred screening test.
 - > the most sensitive marker for iron deficiency
 - Ferritin is an acute phase reactant and may be grossly elevated in the context
 of acute inflammation (when it does not accurately reflect iron stores) and to a
 lesser degree in chronic inflammation.
 - British Society Guidelines on the diagnosis and management or iron deficiency anaemia suggest that:
 - a cut-off of 12-15 mg/L reflects iron deficiency in the absence of inflammation.
 - Where inflammation is present a ferritin of 50 mg/L or more may still be compatible with iron deficiency.

Treatment of IDA

Iron tablet preparations

- Among the tablet preparations, there are:
 - 1. non-enteric coated pills
 - most commonly used as initial treatment due to their lower cost.
 - 2. enteric-coated
 - 3. prolonged-release formulations.
 - Delayed release and enteric-coated iron are better tolerated than the nonenteric coated tablets.
 - less effective since they may contain less iron and their iron may not be released in the duodenum, where iron is absorbed.

- patients who have been treated unsuccessfully with enteric-coated and prolonged-release iron preparations may respond well to the administration of nonenteric-coated ferrous salts
- Ferrous sulphate has more elemental iron by mass than the same dose of ferrous gluconate
- Sustained release preparations may improve tolerance of oral iron but do not aid absorption.

Iron prescription

- Ideally, patients should not take iron supplements within 1-2 hours of antacids → alkaline environment reduces absorption (acidity required for iron solubility)
- Iron tablets are recommended between meals or at bedtime to avoid the alkalinizing
 effect of food and to take advantage of the peak gastric acid production late at night.
- calcium, phosphorus and magnesium salts contained in iron-containing multivitamin pills impair absorption of elemental iron. For this reason, multivitamin preparations should never be recommended as a sole therapy for iron deficient anemia.
- Iron absorption is also delayed with tetracyclines, milk, and phosphate-containing, carbonated beverages such as soft drinks.
- Iron replacement in chronic renal failure
 - ➤ In chronic renal failure, Erythropoeitin (EPO) therapy is only considered in pateints where the ferritin is >100 mg/1.
 - \triangleright If ferritin < 100 → iron replacement is the initial intervention of choice.

IV iron

- Parenteral iron acts no faster than oral iron. It is indicated when oral iron cannot be tolerated or is not absorbed.
- > Indications for IV iron include:
 - unable to tolerate orally,
 - Patients who fail to comply with prescriptions for oral iron supplementation.
 - A history of exertional angina with anaemia → strongest indication for transfusion
 - GIT disorders, such as IBD (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy
 - Iron is poorly absorbed from the GI tract in patients with renal failure, as such IV replacement is the modality of choice.
- It is considered best practice to administer 1000 mg of low molecular weight iron dextran in 250 mL of normal saline in 1 hour without premedication;
- > a test dose of 10 to 25 mg is infused over 3 to 5 minutes prior to the first infusion.
- If no acute reaction is observed, the remaining solution is infused over the balance of 1 hour
- For those with a history of drug allergies or hypersensitivity, 125 mg of methylprednisolone is infused prior to the test dose.

British society of gastroenterology (BSG) guidelines 2011:

- correct anaemia and replenish body stores achieved most simply and cheaply with ferrous sulphate 200 mg twice daily.
- Lower doses may be as effective and better tolerated and should be considered in patients not tolerating traditional doses.
- Other iron compounds (eg, ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better than ferrous sulphate.
- Oral iron should be continued for 3 months after the iron deficiency has been corrected so that stores are replenished.
- Ascorbic acid (250e500 mg twice daily with the iron preparation) may enhance iron absorption
- Iron treatment should follow transfusion to replenish stores.

Anemia of Chronic Disease

Definition

 decreased RBC production due to any longstanding inflammatory, infectious, or malignant disease (includes rheumatoid arthritis, severe trauma, heart disease, diabetes mellitus, and inflammatory bowel disease)

Mechanism of Anemia of Chronic Disease

- there is primarily a decreased availability of iron, relatively decreased levels of erythropoietin, and a mild decrease in the lifespan of RBCs to 70-80 days (normally 120 days)
 - in anemia of chronic kidney disease, ↓erythropoietin production by the interstitial fibroblasts, (also known as type I interstitial cells), → anemia.
 - The kidneys are responsible for approximately 90% of erythropoietin production.
- Increase in hepcidin level in the course of inflammatory disease → ↓release of iron from macrophages + ↓ dietary iron absorption.
 - hepcidin is an acute-phase reactant that is increased in states of inflammation
- cytokines, such as interleukins (IL-1 and IL-6), and tumor necrosis factor (TNF-alpha), →
 destruction of RBC precursors and decrease the number of erythropoietin receptors on
 progenitor cells.

Investigations

- RBCs morphology
 - > normochromic, normocytic anemia.
- Reticulocyte count
 - → \preticulocyte count points to \RBC production as the primary mechanism responsible for anemia,
- ↑ ferritin
- J serum iron
- J TIBC, transferrin saturation, and MCV

Treatment

- treatment of the underlying disease.
- If underlying disease is unknown or treatment of underlying disease does not improve symptomatic anemia
 - > measure EPO
 - if low, administer EPO or erythropoiesis-stimulating agents (ESAs)
 - * make sure iron stores are sufficient
 - if insufficient, patients may be resistant to EPO
 - > if normal, give packed RBCs

Hepcidin

- Hepcidin, a peptide hormone synthesized in the liver.
- reduces extracellular iron in the body by several mechanisms:
 - 1. lowers dietary iron absorption by reducing iron transport across gut mucosal cells (enterocytes);
 - 2. reduces iron exit from macrophages, the main site of iron storage;
 - 3. reduces iron exit from the liver. In all three instances this is accomplished by reducing the transmembrane iron transporter ferroportin.
- inflammation → ↑hepcidin → ↓serum iron due to:
 - > iron trapping within macrophages and liver cells

- decreased gut iron absorption.
- ➤ inadequate amount of serum iron being available for developing red cells →anemia
- hemochromatosis $\rightarrow \downarrow$ hepcidin level \rightarrow iron overload due to:
 - > increased ferroportin mediated iron efflux from storage and increased gut iron absorption.
- Hepcidin inhibits iron transport by binding to the iron export channel ferroportin which is located on the basolateral surface of gut enterocytes and the plasma membrane of macrophages.
 - Inhibiting ferroportin leads to:
 - ↓ iron release from macrophages
 - ↓ dietary iron absorption.

Thalassaemias

Alpha is located on 16, beta on 11chromosome.

Definition

- The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains.
- It is a haemoglobinopathy resulting from defective synthesis of globin chains required for Hb synthesis.
- Each copy of chromosome 16 has two genes for the alpha globin subunit (four in total).
- And each copy of **chromosome 11** has one genes for the **beta globin** subunit (**two in** total).

Types of haemoglobin

Haemoglobin	Chains	% Hb in normal adult
Hb A	$\alpha_2\beta_2$ ((two alpha and two beta chains)	97%
Hb A ₂	$\alpha_2\delta_2$ (two alpha and two delta chains)	< 3.5%
Hb F	α ₂ γ ₂ (two alpha and two gamma chains)	<1%

Alpha-thalassaemia

- Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin
- Alpha-thalassaemia is found in malarial regions of the world (Mediterranean, South-east Asia, Indian sub-continent, Middle East, Sub-Saharan Africa) and should be suspected in patients with these ethnic backgrounds and with microcytosis and/or anaemia.
- Acquired Hb H disease is rare and occurs most commonly in male patients with myelodysplastic syndrome.

Overview

- 2 separate alpha-globulin genes (four in total) are located on each chromosome 16
- There are 4 different alpha-thalassaemias:
 - 1. silent carrier (1 affected alpha-globin gene),
 - 2. alpha-thalassaemia trait (2 affected alpha-globin genes).
 - 3. **Hb H disease** (typically 3 affected alpha-globin genes)
 - 4. **Hb Bart hydrops fetalis syndrome** (typically deletion of all 4 alpha-globin genes).
- Clinical severity depends on the number of alpha chains present
 - If 1 or 2 alpha chains are absent then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal
 - Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly and HbH in red cells. This is known as Hb H disease

- ➢ If all 4 alpha chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)
- Persistence of HbF has survival advantages in severely affected subjects.
- Co-inheritance of alpha-gene mutations, and persistence of fetal haemoglobin production, may restore the globin balance and result in a milder syndrome.
- Features
 - most are asymptomatic.
 - Many patients with Hb H are also clinically well, but are at risk for:
 - acute haemolytic episodes
 - aplastic crises
 - iron overload, even in the absence of chronic transfusions
 - hypersplenism; and
 - endocrine disease.
 - > Hemoglobin gel-electrophoresis
 - α-thalassemia trait → normal
 - 3 gene deletion α -thalassemia \rightarrow HbH $(\beta,\beta,\beta,\beta)$
 - 4 gene deletion α-thalassemia → Hb Barts (v,v,v,v)

Beta-thalassaemia

Disproportionate microcytic anaemia - think beta-thalassaemia trait

If a person has MCV > 80 and MCH > 27, in the absence of symptoms, thalassemia can be reasonably excluded.

Overview

- The most common cause of β- Thalassemia is the defect in **mRNA splicing** of the beta globin gene on <u>chromosome 11</u>.
- · autosomal recessive
- common in Mediterranean populations
- β thalassaemia minor / trait → protects against malaria
 - $\rightarrow \uparrow$ (Hb F) \rightarrow inhibits the development of the malarial parasite.

Types

- β thalassaemia major (β 0):
 - > prevent any formation of β chains,
 - \triangleright the most severe form of β thalassemia.
 - \triangleright 2 gene depletion (β 0 β 0) (α , α , α , α hemoglobin present)
 - aggregation of alpha-globin tetramers → damage erythrocytes →
 extravascular hemolysis.
 - ➤ HbF tries to convert to HbA during first year of life.
 - Fetal hemoglobin is protective in an infant with beta-thalassemia major, hence the disease will only present after six months of age, as its levels decrease.
 - > extramedullary haemopoiesis with hepatosplenomegaly and bone marrow expansion, "hair on end" appearance of bone.
 - Diagnosis
 - Hemoglobin electrophoresis is the best test for diagnosis
 - > Features
 - anaemia
 - splenomegaly
 - occurs secondary to extramedullary hematopoiesis.
 - bone deformities

- ❖ bone marrow expansion can cause "chipmunk facies" or "crew cut sign" on a skull X-ray.
- Target cells on a peripheral blood smear
- early death if not treated appropriately.

> Treatment:

- lifelong regular blood transfusions, (usually every two to five weeks, to maintain the pretransfusion haemoglobin level above 9-10.5 g/dl).
 - transfusion programme with iron chelation is the best initial approach.
- Indications for transfusion:
 - ❖ Hb < 7g/dl on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) or
 - ❖ Hb > 7g/dl with: Facial changes, Poor growth, Fractures, and Extramedullary haematopoiesis
- The transfusional iron overload can be managed with iron chelation, both IV/SC (desferrioxamine) and/or oral (deferasirox).
 - ❖ Desferrioxamine binds iron but needs to be given for 8-12 hours a day for 5-7 days per week, so is a major undertaking for the patient.
 - SE: high frequency deafness, retinopathy and Yersinia infection.
- Stem cell transplantation options offer cure.
- parents and other siblings should be screened by genetic testing.

β thalassaemia intermedia (β+):

- > caused by a mutation in the Kozak consensus sequence of the Beta globin gene on chromosome 11.
- > they allow some β chain formation to occur.
- In either case there is relative excess of α chains, but these don't form tetramers.

β thalassaemia minor / trait:

- 1 gene deletion
- Features
 - usually asymptomatic
 - mild hypochromic, microcytic anaemia microcytosis is characteristically disproportionate to the anaemia (marked microcytosis (very low MCV) (i.e. the Microcytosis is disproportionately with very low MCV for the near normal Hb level >9).
 - **HbA2** $(\alpha_2\delta_2)$ **raised (> 3.5%)** on gel electrophoresis.
 - HbA2 levels above 3.5% are screening criteria for the βthalassemia carrier state.
 - ❖ Note that in cases of severe iron deficiency anaemia the HbA2 may be normal in thalassemia minor.
- Thalassemia can co-exist with other haemoglobinopathies. The most common of these are:
 - > HbE/thalassaemia:
 - common in Cambodia. Thailand, and parts of India
 - clinically similar to β thalassaemia major or thalassaemia intermedia.
 - HbS/thalassaemia:
 - common in African and Mediterranean populations
 - clinically similar to sickle cell anaemia with additional feature of splenomegaly.
 - > HbC/thalassaemia: common in African and Mediterranean populations:
 - HbC/β0 thalassaemia: causes moderate to severe haemolytic anaemia with splenomegaly.
 - HbC/β+ thalassaemia: produce a milder disease.

Beta thalassaemias (reduction in beta globin chains)

Туре	Genotype	Typical findings on CBC	Haemoglobin analysis (HPLC or electrophoresis)
Major (transfusion- dependent)	β ⁰ / β ⁰ or β ⁰ / β ⁺	Severe microcytic anaemia with target cells (typical Hb 3 to 4 g/dL)	HbA₂ (5% or more). HbF (up to 95%). No HbA
Intermedia (non- transfusion- dependent)	β+ / β+	Moderate microcytic anaemia	HbA ₂ (4% or more). HbF (up to 50%)
Minor (also called trait or carrier)	β / β ⁰ or β / β ⁺	Mild microcytic anaemia	HbA ₂ (4% or more). HbF (up to 5%)

β⁰ refers to no beta globin production.

Delta thalassaemia

- about 3% of adult Hb is made of alpha and delta chains.
- mutations can occur which affect the ability of this gene to produce delta chains.

Aplastic anaemia

- Characterised by pancytopaenia and a hypoplastic bone marrow
- Peak incidence of acquired = 30 years old

Features

- Assessment of bone marrow cellularity is best made on trephine biopsy, which often shows replacement of the normal cellular marrow by fatty marrow.
- normochromic, normocytic anaemia
- leukopenia, with lymphocytes relatively spared
- thrombocytopenia
- may be the presenting feature acute lymphoblastic or myeloid leukaemia
- a minority of patients later develop paroxysmal nocturnal haemoglobinuria or myelodysplasia
- In patients with aplastic anemia, the bone marrow is markedly hypocellular.

Causes

- idiopathic
- congenital: Fanconi anaemia, dyskeratosis congenita
- · drugs: cytotoxics, chloramphenicol, sulphonamides, phenytoin, gold
- toxins: benzene
- infections: parvovirus, hepatitis
- radiation

management

Supportive

- blood products
- prevention and treatment of infection

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)

• prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes

β+ refers to decreased beta globin production.

- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

Stem cell transplantation

allogeneic transplants have a success rate of up to 80%

Pure Red Cell Aplasia (PRCA)

Overview

- uncommon disorder
- maturation arrest occurs in the formation of erythrocytes. Erythroblasts are virtually absent in bone marrow; however, white blood cell and platelet production are normal.
- The anemia due to PRCA is usually normocytic but can be macrocytic.

Diagnosis

- · characteristics of PRCA include
 - 1. Severe unexplained anemia
 - 2. ↓Reticulocyte count <1%
 - 3. The presence of less than 0.5% mature erythroblasts in the bone marrow
 - 4. Normocellular bone marrow in most cases

Causes

- most cases of chronic PRCA are idiopathic (acquired primary).
- Secondary PRCA associated with:
 - Autoimmune disorders (eg, type 1 diabetes, thyroiditis, rheumatoid arthritis, Sjögren syndrome)
 - > Thymomas
 - Systemic lupus erythematosus
 - > Hematologic malignancies
 - Solid tumors
 - > Erythropoietin-induced pure red cell aplasia in treatment of CKD anaemia

Treatment

- can be transient and reversible (PRCA due to medications and infections are often reversible.)
- symptomatic anaemia → transfusion
- Treatment of underlying conditions
 - ▶ parvovirus B19 infections → High-dose intravenous immunoglobin
 - ➤ PRCA due to drugs → disappear when the drug is stopped.
 - ➤ thymoma → thymectomy or gamma irradiation of the thymus
- Immunosuppressive:
 - ➤ Corticosteroids are the mainstay of therapy (45% respond) → the first choice
 - > cyclosporine, azathioprine, Cyclophosphamide and rituximab are used

Fanconi's Anaemia

- · Autosomal recessive
- Aplastic anaemia
- ↑ risk of AML
- Neurological manifestation
- Skeletal abnormalities
- Skin pigmentation (café; au lait spots)

Macrocytic anaemia

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

Megaloblastic causes	Non-megaloblastic causes
vitamin B12 deficiencyfolate deficiency	 alcohol liver disease hypothyroidism pregnancy reticulocytosis myelodysplasia drugs: cytotoxics

- If serum folate levels are low, serum vitamin B12 and methylmalonic acid levels should be measured to exclude concurrent vitamin B12 deficiency before folate levels are corrected.
- Normal serum homocysteine levels make folate deficiency unlikely.
- RBC folate is a more accurate indicator of folate deficiency than serum folate level.

Vitamin B12 (cobalamin) deficiency

Function of vitamin B12 deficiency

- Red blood cell development
- Maintenance of the nervous system.
- B12 is necessary for normal folate metabolism, and therefore when there is a primary B12 deficiency, one can see a low red cell folate as a consequence.

Sources

Vit B12 is only found in foods of animal origin e.g. meat, fish and eggs.

Metabolism

- It is absorbed after binding to intrinsic factor (IF) (secreted from parietal cells in the stomach) and is actively absorbed in the **terminal ileum**.
- A small amount of Vit. B12 is passively absorbed without being bound to IF.
- Hepatic stores of vitamin B12 can last for up to 5 years, so it is not uncommon for vegans to display vitamin B12 deficiency years after starting their diet

Causes

- Dietary deficiency of Vit B12: like vegetarians
 - ➤ An MCV of >115 fL is typically seen in nutritional deficiency.
 - very rare
 - Folate deficiency due to dietary problems is common, particularly in the elderly, but it does take many years to become B12 deficient as a result of dietary deficiency.
- Pernicious anaemia
- Post gastrectomy
 - A patient with combined iron deficiency and B₁₂ deficiency, Which operation is he most likely to have had?→ Partial gastrectomy
- Disorders of terminal ileum (site of absorption): Crohn's, blind-loop, Malabsorption of vitamin B-12 secondary to small bowel bacterial overgrowth, tapeworm, etc.
- Bacterial overgrowth syndrome
 - characterized by diarrhea, steatorrhea, and macrocytic anemia.
 - ➤ The common feature is proliferation of colonic bacteria in the small bowel. In normal individuals, the small bowel is relatively sterile.
 - > Common bacteria involved are E.coli or bacteroides.
 - Macrocytic anemia results from increased utilization of vitamin B12 by the colonized bacteria.

- Steatorrhea is caused by reduced concentration of conjugated bile acids. Bacteroides can convert conjugated bile acids to unconjugated bile acids, which result in impaired micelle formation.
- Diarrhea is due to steatorrhea.

Features of vitamin B12 deficiency

- Macrocytic anaemia
- mild jaundice is typical of megaloblastic anaemia (vitamin B₁₂ or folate deficiency) because of increased destruction of red cell precursors in the bone marrow.
- Sore tongue and mouth
- Neuropsychiatric symptoms: e.g. Ataxia, Mood disturbances
 - Neurological involvement can be present in B12 deficiency even in the absence of anaemia, especially in patients over the age of 60.
 - > The peripheral nerves are most commonly involved, followed by subacute degeneration of the spinal cord.
 - > Early signs are loss of peripheral vibration and joint position sense, which is usually followed by loss of reflexes and weakness.
 - The legs and feet are usually more involved than the hands.
 - In the late stages there may be spasticity, upgoing plantars and ataxia but thankfully this is rare in the UK.
- Serum methylmalonic acid levels are elevated in vitamin B12 deficiency.
 - > more sensitive Serum vitamin B12 levels, and should be used to definitively exclude vitamin B12 deficiency.
 - > elevated homocysteine and methylmalonic acid levels.
- Blood smear will show hypersegmented neutrophils.

Treatment

- even in case of profound anaemia, if the patient is not haemodynamically compromised → no need for blood transfusion.
- intramuscular vitamin B₁₂ and oral folic acid.
- Patient need to continue on treatment with ferrous sulphate as iron stores are likely to be depleted rapidly once the marrow starts functioning.
- Giving oral folic acid without vitamin B₁₂ would be hazardous and could precipitate subacute combined degeneration of the spinal cord.

Pernicious anaemia

Epidemiology

- more common in females (F:M = 1.6:1)
- · typically develops in middle to old age
- more common if blood group A

Pathophysiology

- · autoimmune disease caused by antibodies to gastric parietal cells or intrinsic factor
- results in vitamin B12 deficiency
- associated with thyroid disease,
 - diabetes
 - Addison's
 - rheumatoid
 - vitiliao
- · predisposes to gastric carcinoma

Features

- · lethargy, weakness
- dyspnoea
- paraesthesia
- mild iaundice
- diarrhoea
- · sore tongue

- · possible signs:
 - retinal haemorrhages,
 - mild splenomegaly.
 - > retrobulbar neuritis

Investigation

Normal serum gastrin excludes pernicious anaemia

- anti-gastric parietal cell antibodies in 90% (most common, but low specificity)
- anti-intrinsic factor antibodies in 50% (**specific** for pernicious anaemia)
- macrocytic anaemia
- pancytopenia (with low WCC and platelets)
- LDH may be raised due to ineffective erythropoiesis
- also low serum B12.
- hypersegmented polymorphs on film, megaloblasts in marrow
- Schilling test
 - radiolabelled B12 given on two occasions
 - first on its own
 - second with oral IF
 - urine B12 levels measured

macrocytic anaemia and isolated B12 deficiency (folate is normal) suggest an isolated problem with B12 absorption → pernicious anaemia

Management

- If no neurological involvement: 1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months.
- If a patient has deficient in both vitamin B12 and folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration (SCD) of the cord.

Sickle cell disease (SCD)

Overview

- · autosomal recessive
- Sickle cell disease is a haemoglobinopathy caused by the substitution of glutamic acid
 by valine at position 6 (from the N-terminal) of the beta chain. (In sickle cell anaemia,
 valine replaces glutamic acid at the sixth amino acid of the beta globin)
- HbS is caused by a single base mutation on the beta-chain
- The β globin gene is found on the short arm of chromosome 11.

HbS has the following properties:

- contains two α-like globins and two β-like globins and four haem molecules.
- less negatively charged, due to the loss of glutamate for valine.
- has a life span of only 30 days compared to the normal 120 days.
- less soluble than HbA.
- has lower affinity for oxygen than HbA (right-shift of the oxygendissociation curve), which increases the risk of desaturation, but improves the yield of oxygen to the tissues.

- Sickle cell trait: heterozygous (HbAS)
 - occurs when a child inherits a sickle gene from one parent and a normal gene from the other parent.
- Sickle cell disease: homozygous (HbSS)
 - > occurs when a child inherits a sickle gene from each parent.
- Other, rarer forms of sickle cell disease in which the person has only one copy of the mutation that causes Hb S and one copy of another abnormal Hb allele. Examples:
 - "HbSC": (sickle –haemoglobin C disease).
 - "HbS/β+": (sickle-beta-plus-thalassemia).
 - "HbS/β0": (sickle-beta-zero-thalassemia)

Sickling of the erythrocyte

- A low partial pressure of oxygen (PO₂) causes HbS to polymerise and precipitate resulting in sickling of the erythrocyte.
 - HbSS patients sickle at PO₂ of 5-6 kPa
 - ➤ HbAS patients sickle at PO₂ of 2.5-4 kPa.
 - > HbSC Sickling occurs at around 4 kPa.

Sickle cell disease and malaria

- Sickle cell trait (HbAS) is known to protect against falciparum malaria. As a result, the frequencies of sickle cell carriers are high in malaria-endemic areas.
- Patients with HbSS are at higher risk of severe malaria with complications and have a higher mortality rate.

Feature

- Black pigment gallstones occur in 50 % of patients with sickle cell disease
 - due to an increase in bilirubin excretion.
 - Their small size allows migration into the common bile duct causing low-grade obstruction.
 - > Typically leading to hyperbilirubinaemia rather than bile duct dilatation.
 - cholecystectomy is suggested for patients with sickle cell disease if abdominal surgery is being performed for other reasons.
 - ➤ Due to decreased life span of the erythrocyte, average 17 days (normal 120 days), there is also a **chronic circulating unconjugated hyperbilirubinaemia**.
- There is often an inability to concentrate urine
 - The inner medulla is hypoxic, hypertonic and acidotic and therefore predisposes to sickling of red blood cells, which results in vasoocclusion and reduction in renal medullary blood flow.
 - ➤ proximal tubule dysfunction → impairs urinary concentration
 - ➤ distal tubular dysfunction → impairs potassium excretion.
- Functional hyposplenism in SCD also renders sufferers susceptible to infection with encapsulated bacteria (pneumococci, meningococci).
 - Patients with sickle cell disease have a predisposition to develop osteomyelitis due to Salmonella species.

Sickle-cell crises: Four main types of crises are recognised:

- thrombotic crises, also known as painful crises or vaso-occlusive crises
 - precipitated by infection, dehydration, deoxygenation, acidosis, cold temperatures, extreme exercise and stress.
 - infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain

sequestration crises

- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia
- > acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO2 the most common cause of death after childhood
- > stroke
 - 5-10% of sickle cell patients will suffer a stroke, usually during childhood.
 - The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate,
 - prompt institution of a prophylactic transfusion program to reduce the HbS % can prevent further strokes.
 - treatment once occurred → Exchange transfusion programme

aplastic crises

- caused by infection with parvovirus
- > sudden fall in haemoglobin without an appropriate ↑ reticulocytosis.
- The condition is self-limited, with bone marrow recovery occurring in 7-10 days, followed by brisk reticulocytosis.

haemolytic crises

- > rare
- ➤ The anaemia associated with sickle cell disease is usually only symptomatic below 70 g/L, as oxygen is released more readily from erythrocytes.
 - remember, patients with sickle cell tend to run with a Hb between 70-90 g/L normally
- ➤ The anemia of SC is usually a chronic, reasonably well-compensated hemolytic anemia with an appropriate reticulocytosis. For example, the mean hemoglobin and hematocrit concentrations on average may be 79 g/L and 22.9% respectively, with a reticulocyte count of between 3-15%.

Diagnosis of sickle cell disease requires the detection of HbS.

- Sickledex test: addition of reagent to blood → turbidity confirming the presence of HbS, but it gives no information on other haemoglobins.
- Haemoglobin electrophoresis is the only investigation that determines the nature of the haemoglobinopathy
 - > predominance of HbS.
 - Absent HbA.
 - ➤ HbF 2-20%

Treatment

- General management
 - > analgesia e.g. opiates
 - NSAIDs do not usually provide effective analgesia on their own in sickle cell painful crises.
 - > rehydrate
 - oxygen

- consider antibiotics if evidence of infection
- blood transfusion
- exchange transfusion: e.g. if neurological complications

Avoid

- iron therapy: There is a tendency to iron overload and therefore iron therapy is not usually indicated.
- Intra-articular steroids have been associated with a sickle cell crisis, the mechanism of which is not fully understood, but they should be avoided.

pharmaceutical interventions to prevent sickle cell crisis and other acute complications

- Hydroxyurea
 - acts by inhibiting ribonucleotide reductase, which inhibits both purine and pyrimidine synthesis.
 - Action: †fetal haemoglobin (Hb F) which protects against sickling.
 - reduces the incidence of acute chest syndrome and the need for blood transfusion
 - The major side effect is severe myelosuppression.
- > Malaria chemoprophylaxis in endemic area

Acute chest syndrome

- defines as 'an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'.
- management:
 - Oxygen therapy to maintain saturations > 95%
 - Intravenous fluids to ensure euvolaemia
 - Adequate pain relief
 - Incentive spirometry in all patients presenting with rib or chest pain
 - Antibiotics with cover for atypical organisms
 - Early consultation with the critical care team and haematology
 - Blood transfusion:
 - A senior haematologist will make a decision as to whether a simple or exchange transfusion is necessary.
 - guidelines suggest Hb target of 100-110g/L in either instance.
- All adults who have hyposplenism, including patients with SCD, need:
 - Yearly influenza vaccine.
 - Pneumococcal C vaccine, (adults and children over 2 years) repeated every five years.
 - Haemophilus influenzae type b; if not already given as part of childhood immunisation.
 - Conjugated meningococcal C vaccine; if not already given as part of childhood immunisation.
 - Meningococcal ACWY vaccine; if travelling to areas with high risk of meningitis.
- Patients with sickle cell disease are prone to infections within <u>encapsulated organisms</u> because of their asplenic state.
 - > These include:
 - Streptococcus pneumoniae,
 - Haemophilus influenzae and
 - Neisseria meningitidis.
 - > To combat these infections, patients with homozygous sickle cell disease should be on **lifelong penicillin** and be **vaccinated against these organisms**.

Salmonella osteomyelitis is seen in patients with sickle cell anaemia

screening for sickle cell disease in a pregnant women:

- She will first be screened for sickle cell carrier status.
- If that test is positive, her partner will be screened,
- If both are found to be carriers this is confirmed by genetic testing before offering chorionic villus sampling (CVS) (8-10 weeks) or amniocentesis (14-16 weeks).

Priapism

- Priapism is most often due to idiopathic thrombosis of the prostatic venous plexus.
- Other causes include:
 - leukaemia.
 - > sickle-cell anaemia and
 - carcinomatosis.
- Priapism occurs fairly frequently which may lead to permanent impotence if it is not relieved.

Sideroblastic anaemia

Definition

Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose
biosynthesis takes place partly in the mitochondrion. This leads to deposits of iron in the
mitochondria that form a ring around the nucleus called a ring sideroblast.

Causes: It may be congenital or acquired

- Congenital cause: delta-aminolevulinate synthase-2 deficiency
 - > The enzyme delta aminolevulinic acid (ALA) is essential in the biosynthesis of heme.
 - Delta ALA requires <u>pyridoxine</u> (vitamin B6) and <u>copper</u> as cofactors.
 - ➤ Hereditary sideroblastic anemia follows a X-linked genetic inheritance pattern.
- Acquired causes
 - myelodysplasia (seen in older age groups)
 - alcohol
 - the most common reversible cause
 - ▶ lead
 - drugs: anti-TB medications, chloramphenicol.
 - Pyridoxine (vitamin B6) deficiency, caused by <u>isoniazid</u> and oral contraceptives, is a reversible cause of sideroblastic anemia.

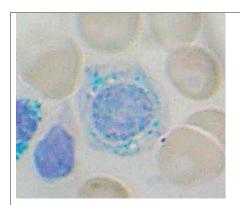
Investigations

- hypochromic microcytic anaemia (more so in congenital)
- Basophilic stippling:
 - visualization of ribosomes on the surface of red blood cells
 - > can be seen on a peripheral blood smear of patients with sideroblastic anemia.
- Ferritin levels are <u>increased</u>
- bone marrow:
 - sideroblasts and increased iron stores
 - Sideroblasts are red cell precursors with iron-laden mitochondria and are detected via Prussian blue staining.
 - Ringed sideroblasts are pathognomonic for sideroblastic anemia.

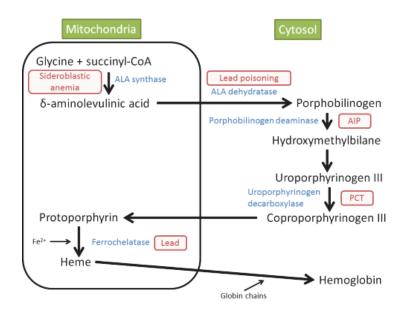
Management

- supportive
- treat any underlying cause

- removal of toxic agents such as zinc and lead, and drugs such as penicillamine and isoniazid.
- pyridoxine may help
- Deposition of iron in secondary haemochromatosis (haemosiderosis):
 - Oral iron chelators
 - First-line : → oral deferasirox
 - Second-line: → Deferiprone
 - side effect: bloody dyscrasias and liver dysfunction.
 - Liver function tests are imperative whilst the patient is being administered both deferiprone and deferasirox.
 - Desferrioxamine results in compliance issues due to the subcutaneous route and long infusion time.
 - Whereas phlebotomy is effective at decreasing iron overload, in a patient who is anaemic this is not a viable option.



The figure illustrates sideroblasts, which are nucleated (immature) erythrocytes with granules of iron in their cytoplasm.



Haemolytic anaemias: by site

The combination of anaemia and jaundice should always suggest haemolytic anaemia until proved otherwise

- In intravascular haemolysis free haemoglobin is released which binds to haptoglobin.
 - > The benefit of this process (Haptoglobin binds with free plasma hemoglobin):
 - permits degradative enzymes access to the hemoglobin,
 - preventing the loss of iron via the kidneys,
 - shielding the kidneys from damage by hemoglobin.
- As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test).
- Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria

Intravascular haemolysis	Extravascular haemolysis
 mismatched blood transfusion G6PD deficiency* red cell fragmentation: heart valves, TTP, DIC, HUS paroxysmal nocturnal haemoglobinuria cold autoimmune haemolytic anaemia 	 haemoglobinopathies: sickle cell, thalassaemia hereditary spherocytosis haemolytic disease of newborn warm autoimmune haemolytic anaemia

^{*}strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause

Haemolytic anaemias: by cause

Hereditary causes

- can be subdivided into membrane, metabolism or haemoglobin defects
 - > membrane: hereditary spherocytosis/elliptocytosis
 - > metabolism: G6PD deficiency
 - haemoglobinopathies: sickle cell, thalassaemia

Acquired causes

- can be subdivided into immune and non-immune causes
 - Acquired: immune causes
 - autoimmune: warm/cold antibody type
 - alloimmune: transfusion reaction, haemolytic disease newborn
 - drug: methyldopa, penicillin
 - ❖ methyldopa → Anti-RBC antibodies
 - ❖ penicillin → reaction between penicillin-like drugs and their antibodies
 - Acquired: non-immune causes
 - microangiopathic haemolytic anaemia (MAHA): TTP/HUS, DIC, malignancy, pre-eclampsia
 - prosthetic cardiac valves
 - paroxysmal nocturnal haemoglobinuria
 - infections: malaria
 - Direct (non-immune) red cell toxicity may occur after lead exposure.

laboratory tests

- Hemoglobin: decreased
- MCV: normocytic
- Reticulocyte count and reticulocyte production index: increased
- Unconjugated bilirubin: increased
- LDH: increased (esp. in intravascular hemolysis)
- Haptoglobin: reduced

Microangiopathic anemia

- The patient's newly diagnosed heart murmur along with new anemia and schistocytes indicate aortic stenosis as the underlying cause.
- Aortic stenosis → mechanical destruction of RBCs (as they travel through the narrowed aortic opening) → microangiopathic anemia
- Schistocytes are fragmented RBCs. Also called helmet cells, they are pathognomic of microagiopathic hemolytic anemias.

Zieve syndrome

- triad of jaundice, hemolytic anemia, and hyperlipidemia.
- Hepatic dysfunction is usually evident in all cases.
- Hemolytic anemia is reversible.
- Hyperlipidemia due to excess alcohol intake causes metabolic and osmotic abnormalities in (RBCs), making them very susceptible to hemolysis.
- Peripheral blood smear reveals:
 - > normocytic normochromic anemia
 - acanthocytes
 - Acanthocytes are also called spur cells.
 - They have multiple projections on their surface caused by hyperlipidemia.
- Definitive treatment → alcohol cessation.

Zieve's syndrome should be suspected whenever there is anemia and elevation of unconjugated bilirubin in the setting of acute alcohol intake with no obvious sign of gastrointestinal bleeding.

Autoimmune haemolytic anaemia (AIHA)

- Autoimmune haemolytic anaemia (AIHA) may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis.
- It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs.
- AIHA is characterised by a positive direct antiglobulin test (Coombs' test)

Warm AIHA

- In warm AIHA the antibody (usually IgG) causes haemolysis best at body temperature and haemolysis tends to occur in extravascular sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy.
- Causes of warm AIHA
 - > autoimmune disease: e.g. systemic lupus erythematosus*
 - SLE can rarely be associated with a mixed-type AIHA
 - > neoplasia: e.g. lymphoma, CLL
 - drugs: e.g. methyldopa, Penicillins, Cephalosporins, levodopa, NSAIDs and Quinidine
 - treated by → stopping the drug ± short course of oral prednisolone.
- The bone marrow respond by increasing RBCs production, which will be evident in peripheral blood by increase in the reticulocytes, immature RBCs, which will have high MCV.
- Management options include steroids, immunosuppression and splenectomy.

- Blood transfusion can be life-saving until immunosuppression can take effect.
- All patients with active haemolysis are at risk of acquiring folate deficiency due to increased metabolic demands and all should receive folic acid replacement therapy.

Cold AIHA

- The antibody in cold AIHA is usually IgM and causes haemolysis best at 4 deg C.
- Haemolysis is mediated by complement and is more commonly **intravascular**.
- Causes of cold AIHA
 - neoplasia: e.g. lymphoma
 - infections: e.g. mycoplasma, EBV
 - Secondary <u>cold agglutinin</u> disease typically presents with anaemia and haemoglobinuria due to intravascular haemolysis two to three weeks following infection such as with:
 - Mvcoplasma pneumoniae
 - Viruses (EBV, CMV, etc)
 - Legionnaires' disease
 - Malaria → The best diagnostic test → Cold agglutinin titre
 - Cold agglutinins occur normally but at very low titres.
- Features may include symptoms of Raynaud's and acrocyanosis
- Patients respond less well to steroids

	Warm AIHA	Cold AIHA
Definition	haemolysis best at body temperature	haemolysis best at 4 deg C
Antibody	IgG	IgM
Site of haemolysis	extravascular (e.g :spleen)	intravascular
Causes	 autoimmune disease: e.g. systemic lupus erythematosus neoplasia: e.g. lymphoma, CLL drugs: e.g. methyldopa 	neoplasia: e.g. lymphoma infections: e.g. mycoplasma, EBV
Treatment	steroids, immunosuppression and splenectomy.	respond less well to steroids

Paroxysmal cold haemoglobinuria (PCH)

- a rare type of autoimmune haemolytic anaemia (AIHA) occurring primarily in children/adolescent.
- The classic symptom is a sudden onset of haemoglobinuria following exposure to cold, even for a few minutes.
- Symptoms may occur minutes to hours following exposure to cold.
- Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis.
- The direct agglutination test (DAT) (Coomb's test) is usually negative.

Cold agglutinin disease

- caused by autoantibodies that react at temperatures < 37 °C,
- typical causes are:
 - lymphoproliferative disorders,
 - infections such as mycoplasma or Epstein–Barr virus.
 - > Around 50% of cases are idiopathic.
 - Non-Hodgkin's lymphoma is more typically associated with cold agglutinins than Hodgkin's.

Hook effect

- Also called or the **prozone effect**
- In agglutination test, a person's serum (which contains antibodies) is added to a test tube, which contains a particular antigen.
- If the antibodies agglutinate with the antigen to form immune complexes, then the test is interpreted as positive.
- However, if too many antibodies are present that can bind to the antigen, then the antigenic
 sites are coated by antibodies, and few or no antibodies directed toward the pathogen are
 able to bind more than one antigenic particle. Since the antibodies do not bridge between
 antigens, no agglutination occurs. Because no agglutination occurs, the test is interpreted
 as negative. In this case, the result is a false negative.
- The range of relatively high antibody concentrations within which no reaction occurs is called the prozone.
- The effect can also occur because of antigen excess, when both the capture and detection
 antibodies become saturated by the high analyte concentration. In this case, no sandwich
 can be formed by the capturing antibody, the antigen and the detection antibody. In this
 case, free antigen is in competition with captured antigen for detection antibody binding.
- Examples include:
- high levels of syphilis antibodies in HIV patients or high levels of cryptococcal antigen leading to false negative tests in undiluted samples.
- This phenomenon is also seen in serological tests for Brucellosis.
- when the serum is diluted, the blocking antibody is as well and its concentration decreases enough for the proper precipitation reaction to occur.

Hereditary spherocytosis

Epidemiology

most common hereditary haemolytic anaemia in people of northern European descent
 Aetiology

autosomal dominant defect of red blood cell cytoskeleton

- the most frequent cause is a mutation in the spectrin gene;
 - > spectrin is a component of the red cell membrane.
- The most common mutation in a Northern European population is a combined spectrin and ankyrin mutation, which is found in 40–65% of patients.
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

Pathophysiology

Genetic mutation → Defects in RBC membrane proteins (especially spectrin and/or ankyrin) responsible for tying the inner membrane skeleton with the outer lipid bilayer → Continuous loss of lipid bilayer components → Decreased surface area of RBCs in relation to volume → Sphere-shaped RBCs with decreased membrane stability → Inability to change form while going through narrowed vessels:

- → Entrapment within splenic vasculature → Splenomegaly
- → Destruction via splenic macrophages → Extravascular hemolysis

Features

Patient with hereditary spherocytosis + acute abdomen → think of: Biliary colic or rupture spleen.

normocytic anaemia, gallstones and family history → hereditary spherocytosis

- failure to thrive
- Congenital skeletal abnormalities (eg, tower-shaped skull, polydactylism) occasionally occur.
- Anemia and pallor
- jaundice (†unconjugated bilirubin)
- gallstones (pigment stones)
 - common and may be the presenting symptom
 - (made of calcium bilirubinate)
 - > may lead to cholecystitis
- Splenomegaly with left upper quadrant pain
- aplastic crisis precipitated by parvovirus infection

Complications

- Aplastic crisis
 - > can be triggered by parvovirus B19 infection.

Investigations

- Normocytic anemia (normal MCV)
- increase in both RDW and MCHC (the high MCHC, indicating hyperdense cells)
- Findings of hemolytic anemia
 - ➤ ↑ Unconjugated bilirubin
 - → LDH
 - ➤ ⊥ Haptoglobin
 - Reticulocytosis
- Direct antiglobulin (direct Coombs) test
 - to exclude autoimmune hemolytic anemia (positive Coombs test), since spherocytosis is seen in both clinical presentations
 - Direct Coombs' test is negative in Hereditary spherocytosis, as it is not an immune haemolysis
- Eosin-5-maleimide binding test (EMA): <u>test of choice</u>, as results are readily available (within two hours)
- Osmotic fragility test (Rupture of Spherocytes in mildly hypotonic solution).
 - unreliable and is no longer recommended in routine clinical practice.
 - this has now been replaced by the eosin-5-maleimide binding to red cells and then being detected by flow cytometry.
- Osmotic gradient ektacytometry
 - used to differentiate hereditary spherocytosis from hereditary stomatocytosis, but is only available in specialised laboratories.
- If the diagnosis is equivocal, the cryohaemolysis test and EMA binding can be used.
- In atypical cases, gel electrophoresis analysis of erythrocyte membranes is the test of choice.
- Blood smear
 - > Characteristic spherocytes (absent central pallor)
 - Potentially anisocytosis
- Ultrasound:
 - to evaluate gallbladder complications

Diagnosis

- The first step in analysis of a spherocytic hemolytic anaemia is → direct antiglobulin test (to determine whether the process is hemolytic or not).
- 2. If negative → confirm HS with other tests.
- The osmotic fragility test is unreliable and is no longer recommended in routine clinical practice.
- 4. Osmotic gradient ektacytometry is used to differentiate hereditary spherocytosis from hereditary stomatocytosis

Management

- · supportive for most patients: folate replacement
- splenectomy
 - best avoided until at least 6 years of age to reduce the risk of post-splenectomy sepsis.
 - It is important to rule out stomatocytosis where splenectomy is contraindicated because of the thrombotic risk.

Hereditary elliptocytosis (HE)

- · autosomal dominant condition.
- Elliptocytosis is usually caused by spectrin and spectrin-protein 4.1 defects.
- Horizontal membrane protein defects (for example, <u>spectrin ankyrin</u> interaction defect) results in HE whereas vertical defects result in hereditary spherocytosis.
- Features
 - Clinical manifestations range from an asymptomatic carriage to severe haemolytic anaemia.
 - Most patients with HE or its variants lead healthy lives.
 - The degree of haemolysis does not correlate with the percentage of elliptocytes seen in the blood.
 - presence of cigar-shaped elliptocytes on the peripheral blood smear (The hallmark of HE)
 - Elliptocytes are normochromic and normocytic and range from few to 100% of erythrocytes.
- Complication
 - > Aplastic crisis
- Treatment
 - Heterozygotes are asymptomatic but show elliptocytes on blood film; they do not have haemolysis and do not require any particular treatment
 - The treatment for symptomatic hereditary elliptocytosis is splenectomy.



Hereditary elliptocytosis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Basics

- (G6PD) plays a vital role in the hexose monophosphate pathway
- It is involved in the oxidation of glucose 6-phosphate to 6-phosphoglycerate. This
 oxidation reaction is needed in RBCs as it provides the only source of NADPH
- NADPH → maintains the level of glutathione → protect the RBCs against oxidative damage from compounds like hydrogen peroxide

Prevalence

- G6PD deficiency is the commonest red blood cell enzyme defect.
- It is more common in people from the Mediterranean, Africa and Chinese

Aetiology

- inherited in a X-linked recessive fashion.
- Homozygotes and heterozygotes can be symptomatic, although the disease typically is more severe in persons who are homozygous for the deficiency.

Factors which Precipitates crisis:

- infections (the most common cause)
- drugs
- broad (fava) beans
 - Favism is most common in persons with G6PD class II variants, but rarely it can occur in patients with the G6PD A–variant (Class III → African descent).
- henna

Pathophysiology

- ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress
- The haemolytic anaemia is **non-immune** (direct antiglobulin test [DAT] negative).

Features

- · usually asymptomatic
- · neonatal jaundice is often seen
- intravascular haemolysis
 - > <u>Decreased haptoglobin levels</u>, hematuria, and presence of <u>urinary hemosiderin</u> indicate severe intravascular hemolysis.
- acute hemolysis can cause back or abdominal pain and jaundice secondary to a rise in unconjugated bilirubin
 - Jaundice, in the setting of normal liver function, typically does not occur until > 50% of the erythrocytes have been hemolyzed.
- gallstones are common
- · splenomegaly may be present
- Heinz bodies (denatured hemoglobin) on blood films

Diagnosis:

- made by using a G6PD enzyme assay
- usually done by fluorescent spot test detecting the generation of NADPH from NADP.
 - The test is positive if the blood spot fails to fluoresce under ultraviolet light.
- In patients with acute hemolysis, testing for G6PD deficiency may be falsely negative because older erythrocytes with a higher enzyme deficiency have been hemolyzed. Young erythrocytes and reticulocytes have normal or near-normal enzyme activity.
- Female heterozygotes may be hard to diagnose because of X-chromosome mosaicism leading to a partial deficiency that will not be detected reliably with screening tests.
- Acute haemolytic reaction
 - ➤ Blood count is normal between attacks of haemolysis
 - During an attack the blood film may show:
 - irregularly contracted cells
 - bite cells

- blister cells
- Heinz bodies
- Reticulocytosis
- Peripheral blood smear → **Heinz bodies** (rarely seen in clinical practice)
- Reticulocyte count: Increases four to seven days after hemolysis
- Haptoglobin → Decreased

Treatment

- avoidance exposure to an oxidative stressor in the form of an infection, oxidative drug, or fava beans
- Acute hemolysis is self-limited, but in rare instances it can be severe enough to warrant a blood transfusion
 - Hemolysis typically occurs 24 to 72 hours after ingestion, with resolution within 4 to 7 days.
- Methaemoglobinaemia in G6PD-deficient patients is best treated with exchange transfusion.

Some drugs causing haemolysis

- · anti-malarials: primaquine
- Quinine/quinidine.
- Ciprofloxacin
- Nitrofurantoin
- chloramphenicol
- **sulph** group drugs: **sulph**onamides, **sulph**asalazine, **sulf**onylureas
- vitamin K, probenecid
- aspirin and (NSAIDs)

Some drugs thought to be safe

- penicillins
- · cephalosporins
- macrolides
- · tetracyclines
- trimethoprim
 - In "Co-trimoxazole": the sulfamethoxazole causes haemolysis in G6PD, not the trimethoprim.

Comparing G6PD deficiency to hereditary spherocytosis:

	G6PD deficiency	Hereditary spherocytosis
Gender	Male (X-linked recessive)	Male + female (autosomal dominant)
Ethnicity	African + Mediterranean descent	Northern European descent
Typical history	Neonatal jaundiceInfection/drugs precipitate haemolysisGallstones	Neonatal jaundice Chronic symptoms although haemolytic crises may be precipitated by infection Gallstones Splenomegaly is common
Blood film	Heinz bodies	Spherocytes (round, lack of central pallor)
Diagnostic test	Measure enzyme activity of G6PD	Osmotic fragility test

Other notes

- G6PD deficiency confers partial protection against malaria
- Hemolysis begins 24 to 72 hours after exposure to oxidant stress.
- Hemolysis due to oxidant stresses are usually self-limiting within 8 to 14 days due to the compensatory production of young red blood cells with high levels of G6PD.
- Young RBCs are not vulnerable to oxidative damage and hence limit the duration of hemolysis.
- G6PD deficiency is an X-linked inherited disease that primarily affects men.
- · Women may be affected if:
 - they are <u>homozygous</u>, which occurs in populations in which the frequency of G6PD deficiency is guite high.
 - > Heterozygous women (carriers) can experience clinical disease as a result of:
 - 1. X chromosome inactivation,
 - 2. gene mosaicism, or
 - 3. hemizygosity
- Severe hemolysis due to G6PD deficiency may manifest as methemoglobinemia

Paroxysmal nocturnal haemoglobinuria (PNH)

The triad of hemolytic anemia, pancytopenia, and thrombosis → PNH

- (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells.
- Caused by increased sensitivity of cell membranes to complement due to a lack of glycoprotein glycosyl-phosphatidyl-inositol (GPI).
- · Patients are more prone to venous thrombosis
- 50% of PNH affected individuals are died due to thrombotic complications

Pathophysiology

- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor CD 55 (DAF) and Membrane Inhibitor of Reactive Lysis CD 59 (MIRL)., are not properly bound to the cell membrane due a lack of GPI
- Hemolysis occurs when patients develop a mild acidosis at night, due to a relative hypoventilation, resulting in the passage of dark urine in the early morning.
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation
- Intrinsic hemolytic anemia with intravascular hemolysis

Features

- symptoms of anemia (Pallor, fatigue, weakness)
- Intermittent jaundice
- haemoglobinuria
 - classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- Abdominal pain
 - > may be due to small mesenteric vein thrombi.

Complications

- thrombosis e.g. Budd-Chiari syndrome
- Vasoconstriction: headache, pulmonary hypertension
- aplastic anaemia may develop in some patients
- ↑ Risk of acute leukemias

Investigations

- ČBC
 - haemolytic anaemia
 - pancytopaenia
- · Dipstick analysis of the urine:

- will be positive for 'blood', but the microscopy will show no red blood cells.
 - This because there is intravascular haemolysis, with intravascular release of haemoglobin. This then passes through the renal tubules, ending up in the urine, and turning the dipstick analysis positive. However, because there are no actual red blood cells in the urine, the microscopy will be negative.
- Flow cytometry (immunophenotyping) of blood
 - absence of CD55 and CD59 on the surface of RBCs
 - now replaced Ham's test as the gold standard investigation in PNH
- Ham's test:
 - acid-induced haemolysis (normal red cells would not)
 - > acidified serum (pH 6.2) is added to blood: PNH cells, but not normal cells, will be lysed.
- Coombs test: negative

Management

- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5 (C5 inhibitor), is reducing intravascular haemolysis
- stem cell transplantation
 - > The gold standard curative treatment

Splenectomy

- Following a splenectomy patients are particularly at risk of infections from:
 - pneumococcus.
 - Haemophilus.
 - > meningococcus and
 - Capnocytophaga canimorsus*(*usually from dog bites)
- Vaccination
 - if elective, should be done 2 weeks prior to operation
 - Hib. meningitis A & C
 - annual influenza vaccination
 - pneumococcal vaccine every 5 years
- Antibiotic prophylaxis
 - > penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

Blood products Whole blood fractions

Fraction	Key points
Packed red cells	 Used for transfusion in chronic anaemia and cases where infusion of large volumes of fluid may result in cardiovascular compromise. Product obtained by centrifugation of whole blood. In a stable patient, red cell packs may be transfused over 90-120 minutes Rapid infusion of red cells or fresh frozen plasma may be required in an acutely bleeding patient but not in patient who is stable.
Platelet rich plasma	 Usually administered to patients who are thrombocytopaenic and are bleeding or require surgery. It is obtained by <u>low speed</u> centrifugation.
Platelet concentrate	 Prepared by <u>high speed</u> centrifugation administered to patients with thrombocytopaenia. the life span of transfused platelets is only 3-7 days. platelet transfusion should not take more than 20-30 minutes. Patients who are refractory to platelet transfusions: should be <u>first</u> investigated to check for adequate platelet rises. This is best done on a one or two-hour post platelet transfusion sample. Further test would include checking for HLA antibodies
Fresh frozen plasma	 Prepared from single units of blood. Contains clotting factors, albumin and immunoglobulin. Unit is usually 200 to 250ml. Usually used in correcting clotting deficiencies in patients with hepatic synthetic failure who are due to undergo surgery. Usual dose is 12-15ml/Kg⁻¹. It should not be used as first line therapy for hypovolaemia.
Cryoprecipitate	 Formed from supernatant of FFP. Rich source of Factor VIII and fibrinogen. Allows large concentration of factor VIII to be administered in small volume.
SAG-Mannitol Blood	Removal of all plasma from a blood unit and substitution with:

Plasma derivatives

- plasma derivatives (such as factor VIII) are prepared from several thousand plasma donations, typically 20,000, or 5,000 kg of plasma at a time.
- Pooled plasma has been sourced from outside the UK since 1999 to avoid vCJD risks.

- > The process involves several chemical steps including:
 - ethanol extraction.
 - chromatography, and
 - viral inactivation steps which results in a freeze-dried product.
- These products have a long shelf life of several months to years.

Cell saver devices

These collect patients own blood lost during surgery and then re-infuse it. There are two main types:

- Those which wash the blood cells prior to re-infusion. These are more expensive to
 purchase and more complicated to operate. However, they reduce the risk of re-infusing
 contaminated blood back into the patient.
- Those which do not wash the blood prior to re-infusion.

Their main advantage is that they avoid the use of infusion of blood from donors into patients and this may reduce risk of blood borne infection. It may be acceptable to Jehovah's witnesses. It is contraindicated in malignant disease for risk of facilitating disease dissemination.

Blood products used in warfarin reversal

Immediate or urgent surgery in patients taking warfarin:

- 1. Stop warfarin
- 2. Vitamin K (reversal within 4-24 hours)
 - IV takes 4-6h to work (at least 5mg)
 - Oral can take 24 hours to be clinically effective
- 3. Fresh frozen plasma
 - Used less commonly now as 1st line warfarin reversal
 - 30ml/kg⁻¹
 - Need to give at least 1L fluid in 70kg person (therefore not appropriate in fluid overload)
 - Need blood group
 - Only use if human prothrombin complex is not available
- 4. Human Prothrombin Complex (reversal within 1 hour)
 - Bereplex 50 u/kg
 - Rapid action but factor 6 short half life, therefore give with vitamin K

Neonatal exchange transfusion

- An exchange transfusion requires blood which is plasma reduced whole blood in CPD (citrate phosphate dextrose/anticoagulant), irradiated and less than five days old.
- The Rh group should either be Rh negative or identical to the neonate, to avoid haemolytic transfusion reaction in the neonate.

Blood Transfusion Thresholds

■ Sepsis: 7 g/dL

■ Upper or lower GI bleeds: 7 g/dL ■ Acute neurologic injury or TBI: 7 g/dL

■ Stable CV disease: 8 g/dL

■ ACS: 10 g/dL

Blood product transfusion complications

Complications

- haemolytic: immediate or delayed
- · febrile reactions
- transmission of viruses, bacteria, parasites, vCJD
- hyperkalaemia
- · iron overload
- ARDS
- clotting abnormalities

Immediate haemolytic reaction

- occur during the transfusion.
- e.g. ABO mismatch
- massive intravascular haemolysis

Delayed haemolytic transfusion reaction

- occurs 24 hours after the transfusion.
- This happens in a patient who has been previously immunised by transfusions or pregnancy. The antibodies are not detectable initially but become obvious as a secondary immune response to the antigen exposure during the transfusion occurs.

Febrile reactions

- due to anti HLA antibodies in recipient serum or granulocyte specific antibodies (for example, sensitisation during previous pregnancy or previous blood transfusion).
- Febrile non-haemolytic reactions are very common and are due to the presence of pyrogenic cytokines released from leucocytes during storage of the blood units.
 - > apart from a mild fever, the patient is very well.
 - rapid rise in temperature may be due to ABO incompatibility, but With ABO incompatibility patients become shocked very quickly.

Rhesus D mismatch

- It is very often necessary to give D positive platelets to D negative people due to platelet shortage.
- If the recipient of this mismatch is a female of child bearing age, then prophylactic anti- D should be administered with the platelets to prevent production of immune anti- D.
- If anti-D does not administered, the immune anti-D she has made can cross the placenta when she become pregnant in the future and cause haemolytic disease of the fetus/newborn, if the baby is D positive, and this can be life threatening to the baby.
 - > Advise patient that this is only likely to be of consequence should she become pregnant in the future.

Causes a degree of immunosuppression

 e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not

The risk of viral transmission

- A broad knowledge of the risks may be required while consenting a patient for blood transfusion.
- in the United Kingdom, the risks;
 - > For hepatitis B are 1 per 1.3 million donations
 - For HIV are 1 in 6.5 million and
 - For hepatitis C 1 in 28 million donations.

Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
- — from late 1999 onward, all donations have undergone removal of white cells
 (leucodepletion) in order to reduce any vCJD infectivity present

- →from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
- → from 2004 onward, recipients of blood components have been excluded from donating blood

iron overload

- secondary to chronic blood transfusion (eg: in myelodysplastic syndrome)
- · early signs:
 - grey skin
 - > early hear failure
 - diabetes
- treatment:
 - iron chelation with desferrioxamine subcutaneously
 - bind iron
 - ❖ needs to be given for 8 12 hours a day for 5 7 days per week
 - common side effects of desferrioxamine:
 - high frequency deafness
 - retinopathy
 - Yersinia infection

irradiated blood products

- the advantage of irradiated red cells
 - > Inactivates donor lymphocytes
- Indications for irradiated blood products
 - Those at risk of transfusion associated with graft versus host disease such as neonates
 - Those receiving purine analogues-based chemotherapy
 - > Hodgkin's lymphoma
 - Immunodeficiency states
 - Post bone marrow transplants

Pre-operative request for the blood bank for elective surgeries

- Group and save only
 - ➤ A 'group and save' is adequate for elective surgeries and is standard practice in most modern blood banks. This will involve blood grouping and its confirmation as well as an antibody screen.
 - Other options include cross match and a direct Coombs' test are not routinely done for elective surgery

Transfusion errors

 Mislabelling of samples, requests, or wrongly identifying recipients are the commonest transfusion errors.

January 2016 exam: What is the risk of variant Creutzfeldt-Jakob Disease (vCJD) transmission via blood transfusion?

→ Measures are taken to reduce the risk of vCJD transmission but there remains a very small risk of transmission

Transfusion Related Acute Lung Injury (TRALI)

Definition

 (TRALI) is a rare but serious syndrome characterized by sudden acute respiratory distress within six hours after blood product administration

Risk factors

- Caused by anti-HLA, Human Neutrophil Antigens (HNA) or anti-granulocytes antibody in donor blood.
- Donor's blood sensitization occurs in:
 - ➤ Multiparous ♀ develop these antibodies through exposure to fetal blood
 - Previous transfusion
 - Transplantation patient
- When blood is obtained from above mentioned donors, it carries higher risk for recipient to develop TRALI; those who have lung pathology are more susceptible. TRALI symptoms resemble ARDS.

Pathophysiology

- transfused human leukocyte or neutrophil antigen (HLA or HNA) antibodies → activation of donor neutrophils → Neutrophils adhere to pulmonary endothelium to increase permeability and cause pulmonary edema.
- Patients with certain clinical conditions (eg, infection, inflammation, surgery) have primed neutrophils that are susceptible to activation by transfused bioactive substances.
- TRALI has two proposed pathophysiologic mechanisms:
 - **1.** the antibody hypothesis. (antigen-antibody interactions)
 - ➤ The human leukocyte antigen (HLA class I, HLA class II) or human neutrophil antigen (HNA) antibody in the transfused component reacts with neutrophil antigens in the recipient The recipient's neutrophils lodge in the pulmonary capillaries and release mediators that cause pulmonary capillary leakage.
 - > As a consequence, many patients with TRALI will develop transient leukopenia.
 - However, transfusions of blood components containing neutrophil antibodies may cause leukopenia, that do not meet the definition of TRALI.
 - 2. The neutrophil priming hypothesis:
 - does not require antigen-antibody interactions
 - > occurs in patients with clinical conditions that predispose to neutrophil priming and endothelial activation such as infection, surgery, or inflammation.
 - ➤ Bioactive substances in the transfused component activate the primed, sequestered neutrophils, and pulmonary endothelial damage occurs.
- Both mechanisms lead to pulmonary edema in the absence of circulatory overload.

Feature

- Occurring within 1 to 6 hours of transfusion of plasma-containing blood components.
- Patients present with the rapid onset of dyspnea and tachypnea.
- There may be associated fever, cyanosis, and hypotension.
- Clinical examination reveals hypoxic respiratory distress, and pulmonary crackles may be present without signs of congestive heart failure or volume overload.
- Chest x-ray (CXR) shows evidence of bilateral pulmonary edema unassociated with heart failure (non-cardiogenic pulmonary edema), with bilateral patchy infiltrates, which may rapidly progress to complete "white out" indistinguishable from acute respiratory distress syndrome (ARDS).
- Physiologic findings include acute hypoxemia with PaO2/FiO2 less than 300 mmHg and normal cardiac function on echocardiogram.

Diagnosis:

· confirmed by finding of anti-HLA or anti-Neutrophil antibody in donors' or recipient blood.

Treatment

- Early and intensive pulmonary support reduces the risk of a fatal outcome.
- Since the pulmonary edema in TRALI is not related to fluid overload or cardiac dysfunction, but to altered vascular permeability in the lungs with exudation of fluid and protein into the alveoli, it is logical that:
 - maintenance of adequate circulating volume is the most beneficial and appropriate therapy.
 - > Corticosteroids,
 - > epinephrine
 - > and also ventilatory support are treatment options.

How to distinguish TRALI and ARDS from Pulmonary oedema?

- In the exam take into account the clinical findings and scenario to distinguish.
- The hallmark of ARDS is refractory hypoxia with non-cardiogenic pulmonary edema
- Normal pulmonary capillary wedge pressure is between 5 15 mmHg. A PCWP exceeding 15 mmHg suggests mitral stenosis, mitral insufficiency, severe aortic stenosis, aortic regurgitation, ventricular failure, or other cardiac defects or pathologies.
- When the PCWP exceeds 20 mmHg, the transmission of this pressure back into the pulmonary vasculature increases pulmonary capillary hydrostatic pressure which can lead to pulmonary oedema.

Graft versus host disease (GVHD) See transplant topic in renal system

Plasma exchange

Indications for plasma exchange (also known as plasmapheresis)

- Guillain-Barre syndrome
- · myasthenia gravis
- Goodpasture's syndrome
- ANCA positive vasculitis e.g. Wegener's, Churg-Strauss
- TTP/HUS
- crvoglobulinaemia
- hyperviscosity syndrome e.g. secondary to myeloma

Deep vein thrombosis (DVT)

Cancer patients with VTE - 6 months of LMWH

Venous thromoboembolism - length of warfarin treatment

- · provoked (e.g. recent surgery): 3 months
- unprovoked: 6 months

DVT Risk Factors:

- Hematological
 - > Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
 - Polycythemia
 - Paroxysmal nocturnal hemoglobinuria
 - Hyperviscosity syndrome

Autoimmune

- > Antiphospholipid syndrome
- Behcet's

Drugs

- Combined oral contraceptive pill: 3rd generation more than 2nd generation
- > Antipsychotics (especially olanzapine) have recently been shown to be a risk factor

· Other conditions

Homocystinuria

Diagnosis

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

Two-level DVT Wells score

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2

Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test and if it is positive arrange:
- a proximal leg vein ultrasound scan within 4 hours
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

Management

Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed.

• a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis

- the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range
- warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment'
- NICE add 'consider extending warfarin beyond 3 months for patients
 withunprovoked proximal DVT if their risk of VTE recurrence is high and there is no
 additional risk of major bleeding'. This essentially means that if there was no obvious cause
 or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a
 tendency to thrombosis and should be given treatment longer than the norm of 3 months. In
 practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE
- for patients with active cancer NICE recommend using LMWH for 6 months
- for patients with active ulcerative colitis who developed DVT
 - > may require Emergency colectomy, as such warfarinisation would be inappropriate.
 - should be heparinised as this would be easily reversible if it needs to be discontinued prior to surgery or if severe worsening of bleeding occurs.

Time of starting prophylaxis in elective knee replacement surgery:

- LMWH or fondaparinux (s/c factor X inhibitor) → should be started 6 12 hours after surgery
- Dabigatran (oral factor X inhibitor) → 1 4 hours after surgery

Unprovoked VTE

- → (Malignancy investigations and thrombophilia screening)
- As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots.

Malignancy investigations

- Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:
 - > a physical examination (guided by the patient's full history) and
 - a chest X-ray and
 - blood tests (full blood count, serum calcium and liver function tests) and urinalysis.
- Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE

Thrombophilia screening

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

The next most important investigation:

- Unprovoked VTE → chest X-ray, blood tests and urinalysis
- Unprovoked VTE + family history of VTE → Thrombophilia screening

Pregnancy: DVT/PE

Coagulation elements in pregnancy:

- Increased → factors VII, VIII, IX, X, and XII, fibrinogen, plasminogen, and D-dimer.
- Decreased → factor XI and protein S.
- Not changed → Factor II, protein C, and anti-thrombin III.

Overview

- pregnancy is a hypercoagulable state
- majority occur in last trimester

Pathophysiology

- increase in factors VII, VIII, X and fibrinogen
- · decrease in protein S
- uterus presses on IVC causing venous stasis in legs

Management

- · warfarin contraindicated
- S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

Post-thrombotic syndrome

- It is increasingly recognised that patients may develop complications following a DVT.
- Venous outflow obstruction and venous insufficiency result in chronic venous hypertension.
- The resulting clinical syndrome is known as post thrombotic syndrome.

Features

- painful, heavy calves
- pruritus
- swelling
- varicose veins
- · venous ulceration

Management

- Compression stockings should be offered to all patients with deep vein thrombosis to help reduce the risk of post-thrombotic syndrome.
- NICE state the following:
 - Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and:
 - advise patients to continue wearing the stockings for at least 2 years
 - ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions
 - advise patients that the stockings need to be worn only on the affected leg or legs.

<u>Venous thromboembolism: prophylaxis in patients admitted to</u> hospital

Venous thromboembolism (VTE) still accounts for a significant proportion of avoidable hospital deaths. In an effort to tackle this problem NICE produced guidelines in 2010.

Before admission

 advise women to consider stopping oestrogen-containing oral contraception or HRT 4 weeks before surgery. assess the risks and benefits of stopping antiplatelet therapy 1 week before surgery.

The following patients are deemed at risk of VTE

Medical patients

- if mobility significantly reduced for >= 3 days or
- if expected to have ongoing reduced mobility relative to normal state plus any VTE risk factor (see below)

Surgical patients and patients with trauma

- if total anaesthetic + surgical time > 90 minutes or
- if surgery involves pelvis or lower limb and total anaesthetic + surgical time > 60 minutes or
- if acute surgical admission with inflammatory or intra-abdominal condition or
- if expected to have significant reduction in mobility or
- if any VTE risk factor present (see below)

VTE risk factors

- · active cancer or cancer treatment
- age > 60 years
- · critical care admission
- dehydration
- known thrombophilias
- obesity (BMI > 30 kg/m²)
- one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- personal history or first-degree relative with a history of VTE
- · use of HRT
- · use of oestrogen-containing contraceptive therapy
- · varicose veins with phlebitis

In-patient VTE prophylaxis

As a general rule pharmacological VTE prophylaxis is used for medical patients unless there is a contraindication.

For surgical patients mechanical VTE prophylaxis is offered for patients at risk. Pharmacological VTE prophylaxis is also given for if the risk of major bleeding is low.

Pharmacological VTE prophylaxis options:

- fondaparinux sodium
- low molecular weight heparin (LMWH)
- unfractionated heparin (UFH) (for patients with renal failure)

Mechanical VTE prophylaxis options:

- anti-embolism stockings (thigh or knee length)
- · foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

Post-procedure VTE prophylaxis

For certain procedures pharmacological VTE prophylaxis is recommended for all patients, using one of the following:

- dabigatran, started 14 hours after surgery
- fondaparinux, started 6 hours after surgery
- LMWH, started 6-12 hours after surgery
- rivaroxaban, started 6-10 hours after surgery.
- Apixaban

Procedure	Length of prophylaxis
Elective hip	28-35 days
Elective knee	10-14 days
Hip fracture	28-35 days

Superficial thrombophlebitis

- Superficial thrombophlebitis, as the name suggests describes the inflammation associated with thrombosis of one of the superficial veins, usually the long saphenous vein of the leg.
- This process is usually non-infective in nature but secondary bacterial infection may rarely
 occur resulting in septic thrombophlebitis.
- Around 20% with superficial thrombophlebitis will have an underlying deep vein thrombosis (DVT) at presentation and 3-4% of patients will progress to a DVT if untreated.
- The risk of DVT is partly linked to the length of vein affected an inflammed vein > 5 cm is more likely to have an associated DVT.

Management

- Traditionally NSAIDs have been used, with topical NSAIDs for limited and mild disease and oral NSAIDs for more severe disease.
- Topical heparinoids have also be used in the management of superficial thrombophlebitis.
- A Cochrane review however found topical NSAIDs and heparinoids have no significant benefit in terms of reducing extension or progression to DVT.
- Oral NSAIDs were however shown to reduce the risk of extension by 67%.
- Compression stockings are also used.
- Remember that the ankle-brachial pressure index (ABPI) should be measured before
 prescribing compression stockings, particularly if using class 2 or above stockings.
- One of the major changes to the management of superficial thrombophlebitis is the increased use of low-molecular weight heparin. This has been shown to reduce extension and transformation to DVT.
- SIGN produced guidelines in 2010:
 - Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT.
 - ➤ Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days.
 - If LMWH is contraindicated, 8-12 days of oral NSAIDS should be offered.
 - Patients with superficial thrombophlebitis at, or extending towards, the sapheno-femoral junction can be considered for therapeutic anticoagulation for 6-12 weeks.
- This may be a significant departure from our current practice the majority of patients with superficial thrombophlebitis (i.e. those affecting the long saphenous vein) should be referred for an ultrasound scan.

Thrombophilia: causes

inherited thrombophilias:

- the most common → Factor V Leiden
- the higher risk of VTE → Anti-thrombin III deficiency

Inherited thrombophilias

- Gain of function polymorphisms
 - factor V Leiden (activated protein C resistance): most common cause of thrombophilia
 - > prothrombin gene mutation: second most common cause
- Deficiencies of naturally occurring anticoagulants
 - > antithrombin III deficiency
 - ▶ protein C deficiency → Reduced degradation of factors Va and Villa

protein S deficiency

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

Condition	Prevalence	Relative risk of VTE
Factor V Leiden (heterozygous)	5%	4
Prothrombin gene mutation (heterozygous)	1.5%	3
Protein C deficiency	0.3%	10
Protein S deficiency	0.1%	5-10
Antithrombin III deficiency	0.02	10-20

Acquired thrombophilias:

- Antiphospholipid syndrome
- Drugs
 - the combined oral contraceptive pill

NICE recommend testing for thrombophilia in case of unprovoked venous thromboembolism and family history.

Indications of thrombophilia testing: Thrombophilia testing is considered useful in patients presenting with:

- A first episode of venous thromboembolism (VTE) at a young age (usually considered less than 45 years of age)
- Idiopathic venous thrombosis
- A family history of thrombosis, particularly in a first degree relative
- VTE in an unusual vascular territory
- Neonatal purpura fulminans
- Warfarin induced skin necrosis

Factor V Leiden

Activated protein C resistance (Factor V Leiden) is the most common inherited thrombophilia

Factor V Leiden mutation results in activated protein C resistance

Epidemiology

- Factor V Leiden (activated protein C resistance) is the most common inherited thrombophilia, being present in around 5% of the UK population.
- present in 5-9% of the European population but is rare in people of Asian and African descent.

Aetiology

- It is due to a mutation in the Factor V Leiden mutation.
- mostly inherited in an autosomal dominant fashion

 caused by an amino acid substitution results in replacement of arginine with <u>glutamine</u> in the amino acid chain, that impairs the ability of activated protein C and S to inactivate factor Va.

Pathophysiology

- Normally, activated protein C inactivates factor V in the clotting cascade → decreases the
 activation of thrombin.
- However, in patients with these defects, factor V remains active → activates prothrombin → increases thrombotic events.

Features

- results in a 30% lifetime risk of VTE for homozygotes and 5-10% for heterozygotes.
- Heterozygotes have a 4-5 fold risk of venous thrombosis.

Diagnosis

- The gold standard for the diagnosis of factor V Leiden is genetic testing for the mutation.
 Management
 - · prophylaxis against thromboembolism.
 - Contraceptive medications and devices that contain the hormone estrogen should not be used.
 - > Non-hormonal and progesterone-only methods are safe for use in these patients
 - patients with no history of VTE are not indicated for prolonged anticoagulation prophylaxis.

Protein C deficiency

- Protein C deficiency is an <u>autosomal codominant</u> condition which causes an increased risk of thrombosis
- · Protein C is synthesized in the liver.
- It is a relatively common thrombophilia disorder, affecting 1 in 500 individuals.

Function of protein C

inactivation of factors Va and VIIIa.

Features

- · venous thromboembolism
- skin necrosis following the commencement of warfarin:
 - when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
 - The best initial step for the management of warfarin-induced skin necrosis is stopping warfarin.

Diagnosis

- Copperhead snake venom assay
 - > the best test to detect protein-C deficiency

Management

 Patients with a history of a thrombotic event should receive prophylactic anticoagulation for <u>life</u>.

What pathological process is most likely to be responsible for increased propensity to clot in a patient diagnosed with protein C deficiency?

→ Reduced degradation of factors Va and VIIIa

Antithrombin III deficiency

- Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population.
- Inheritance is autosomal dominant

Function of Antithrombin III

- Antithrombin III inhibits several clotting factors, primarily thrombin, factors II, IX, and X.
 - the affinity of Antithrombin III for <u>Factor II and X</u> is much greater, and it thus has a much stronger inactivation effect on these factors.
- It mediates the effects of heparin

Features

- · recurrent venous thromboses
- arterial thromboses do occur but are uncommon

Diagnosis

The best initial test for diagnosing antithrombin III deficiency is <a href="https://two.ncbi.nlm.nitial.nit

Management

- thromboembolic events are treated with lifelong warfarinisation
- heparinisation during pregnancy*
 - *as patients with antithrombin III deficiency have a degree of resistance to heparin, anti-Xa levels should be monitored carefully to ensure adequate anticoagulation
- antithrombin III concentrates (often using during surgery or childbirth)

Hereditary haemorrhagic telangiectasia (HHT)

Hereditary haemorrhagic telangiectasia - autosomal dominant

- Also known as Osler-Weber-Rendu syndrome
- characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes.

Genetic

- autosomal dominant
- Two genes: ENG (endoglin) and ALK-1 (activin receptor like kinase-1) encode proteins expressed on vascular endothelial cells. Mutations in these genes cause an imbalance in angiogenesis.

Epidemiology

- occurs in approximately 1 in 5000 of the population.
- 20 % of cases occur spontaneously without prior family history.
- commonly presents in teenagers. 62% are diagnosed by age 16.

Features and complications

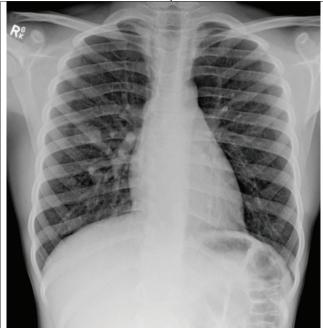
- over 90% present with nosebleeds (the most common initial mode of presentation)
- GI telangiectasias and arteriovenous malformations (AVMS) may cause chronic slow bleeding leading to iron deficiency anemia
- AVMS in the respiratory system may cause <u>dyspnoea and cyanosis and paradoxical</u> <u>cerebral emboli.</u>
- GI telangiectasias and arteriovenous malformations may cause acute haemorrhage
- In the brain AVMS, angiomas and aneurysms may lead to **stroke**

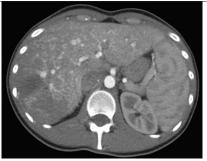
Diagnosis

• There are 4 main diagnostic criteria (Curacao criteria).

- 1. epistaxis: spontaneous, recurrent nosebleeds
- 2. telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- 3. visceral lesions: for example, gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- 4. family history: a first-degree relative with HHT

 The diagnosis is <u>definite</u> if 3 criteria are present, <u>suspected</u> with 2 criteria and <u>unlikely</u> if fewer than 2 criteria are present.





The CT scan shows multiple hepatic arteriovenous malformations

The chest x-ray shows **multiple pulmonary nodules** representing arteriovenous malformations, the largest in the right mid-zone.



Mucocutaneous telangiectasias involve the lips (HHT)



The slide shows the typical appearance of hereditary haemorrhagic telangiectasia (also known as Osler-Weber-Rendu disease)

Idiopathic thrombocytopenic purpura (ITP)

ITP - give oral prednisolone

- ITP is an immune mediated reduction in the platelet count.
- Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.
- Most often the stimulus is unknown, but it can be secondary to other autoimmune disorders (e.g. SLE), viral infections (e.g. CMV, VZV, hepatitis C, HIV), Helicobacter pylori, medication and lymphoproliferative disorders.
- It results in **isolated thrombocytopenia**, with the most common presenting sign being a purpuric rash.
- ITP can be divided into acute and chronic forms:

Acute ITP

- · more commonly seen in children
- · equal sex incidence
- · may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

Chronic ITP

- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Evan's syndrome

• ITP in association with autoimmune haemolytic anaemia (AIHA)

Investigations

- antiplatelet autoantibodies (usually IgG)
- bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

Management

- · No treatment is an option if asymptomatic.
- oral prednisolone (80% of patients respond)
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

Prognosis

• The principal cause of death in patients with ITP is intracranial haemorrhage

Langerhans cell histiocytosis Also called (Eosinophilic granuloma, Histiocytosis X)

Definition

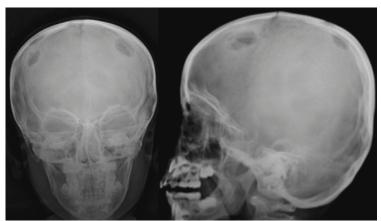
- Abnormal proliferation of pathogenic Langerhans cells (dendritic cells found in the skin) in single or multiple organs. This leads to inflammation and tissue destruction in different organs of the body
- It is the most common type of histiocytosis (i.e., syndrome characterised by the abnormal proliferation of histiocytes).

Pathophysiology

- Exact aetiology and pathogenesis is unknown;
- thought to be either a malignant process or due to immune dysregulation

Features

- more frequent in children (< 15 year)
 - typically presents in childhood with bony lesions
- bone pain, (present in 80% of patients, and are commonly seen on scalp) typically in the skull or proximal femur
- · skin rash, cutaneous nodules
- Cranial involvement: Diabetes insipidus → polyurea and polydipsia (common in patients with multi-system disease)
- · recurrent otitis media/mastoiditis
- GIT involvement : hepatosplenomegaly



Young girl with multiple well defined 'punched out' osteolytic lesions with scalloped edges (geographic skull) are seen in the bilateral parietal regions. The lesions have a characteristic bevelled edge.

Diagnostics

- X-ray: osteolytic lesions
- Tissue biopsy of lesion (confirmatory test):
 - ➤ on electromicroscopy → tennis racket-shaped Birbeck granules
 - proliferation of Langerhans cells; polygonal cells with coffee-bean shaped nuclei, eosinophilic cytoplasm, and Birbeck granules
 - presence of CD1a and langerin (CD207) or Birbeck granules is definitive for diagnosis.

Treatment

• Multi-system disease is treated with systemic, multi-agent chemotherapy.

Myelofibrosis

Myelofibrosis - most common presenting symptom - lethargy

Tear-drop poikilocytes = myelofibrosis

Overview

- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen
- commonly associated with the JAK2 kinase mutation.

Features

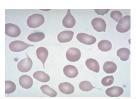
- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- · massive splenomegaly
 - (due to extramedullary hematopoiesis)
- · hypermetabolic symptoms: weight loss, night sweats etc

Complications

• Myelofibrosis can change to acute myeloid leukaemia.

Laboratory findings

- anaemia
- high WBC and platelet count early in the disease
- · 'tear-drop' poikilocytes on blood film
- unobtainable bone marrow biopsy 'dry tap' therefore trephine biopsy needed
 - bone marrow biopsy is characterized by excessive proliferation of megakaryocytes.
- high urate and LDH (reflect increased cell turnover)



Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis

Treatment

· Bone marrow transplant is the only curative treatment

Myelodysplastic syndrome (MDS)

Overview

- · premalignant condition.
- primarily affects elderly people (> 60).
- more common in males than in females

Pathophysiology

- clonal mutation predominates in the bone marrow, suppressing healthy stem cells.
- the main cause of cytopenias
 - In the early stages of MDS → increased apoptosis (programmed cell death).
 - ➤ As the disease progresses and converts into leukemia, → proliferation of leukemic cells overwhelms the healthy marrow.

Causes

- primary or idiopathic MDS (80%)
- genetic predisposition
- hematopoietic stem cell injury caused by exposure to any of the following:
 - Cytotoxic chemotherapy
 - > Radiation
 - Viral infection
 - Genotoxic chemicals (eg, benzene)

Features

macrocytic anaemia, thrombocytopenia and neutropenia with a small number of circulating blasts \rightarrow suggests a diagnosis of myelodysplastic syndrome

- 80% of patients present because of symptoms of anaemia (fatigue and malaise)
- Petechiae, ecchymoses, and nose and gum bleeding are common manifestations of a low platelet count.
- neutropenia may leads to fever and infections
- blood film:
 - dimorphic picture (some red cells are hypochromic and microcytic, while others appear macrocytic)
 - neutrophils are hypogranular and hyposegmented (Pelger-Huet cells).
 - > The peripheral blood count may show;
 - single cytopenia (anemia, thrombocytopenia, or neutropenia) in the early phase or
 - bicytopenia (2 deficient cell lines) or
 - pancytopenia (3 deficient cell lines) in later stages.
 - > unexplained macrocytic anemia with no evidence of megaloblastic anemia
- Bone marrow aspirate stained with Perls' stain showed ring sideroblasts
 - Ring sideroblasts contain an abnormally high concentration of iron, usually stored in perinuclear mitochondria.
 - Perls' stain (which stains for iron) shows this iron deposition as a dark ring around the margin of the nucleus.
 - Cytogenetic studies of the bone marrow cells:
 - Chromosomal abnormalities are clonal and include 5q-, monosomy 7 (-7) or 7q-, trisomy 8 (+8),
 - Multiple combinations indicates a very poor prognosis.
 - A single abnormality, except those involving chromosome 7, indicates good prognosis.

Classification

- The (French-American-British (FAB) system classifies MDS into the following five subgroups:
 - Refractory anemia (RA)
 - RA with ringed sideroblasts (RARS)
 - RA and RARS are characterized by ≤ 5% myeloblasts in bone marrow.
 - RARS is defined morphologically as having 15% erythroid cells with abnormal ringed sideroblasts,
 - Both RA and RARS have a prolonged clinical course and a low prevalence of progression to acute leukemia.
 - progression to acute leukemia occurred in 5% of RARS cases, compared with 25% of RAEB cases
 - > RA with excess blasts (RAEB; 6-20% myeloblasts)
 - ➤ RAEB in transition to AML (RAEB-T; 21-30% myeloblasts)

- acute myeloid leukemia (AML: >30%).
- Chronic myelomonocytic leukemia (CMML)
 - manifests as
 - monocytosis of ≥1000/µL.
 - ♦ total white blood cell (WBC) count of < 13,000/µL, and</p>
 - trilineage dysplasia.
 - CMML must be differentiated from classic chronic myelocytic leukemia, which is characterized by a negative Ph chromosome.
- WHO classification 2008:
 - > Refractory anaemia with unilineage dysplasia- ie anaemia, neutropaenia or thrombocytopaenia (<5% blasts)
 - Refractory anaemia with ring sideroblasts (<5% blasts; >15% sideroblasts)
 - Refractory anaemia with multilineage dysplasia (based on bone marrow dysplasia in 2 or more myeloid lineages)
 - Refractory anaemia with excess blasts-1(5-9% blasts) and refractory anaemia with excess blasts -2 (10-19%)
 - Blasts > 20% is now classified as acute myeloid leukaemia.
 - Myelodysplasia unclassified
 - Myelodysplasia with isolated 5qdel(cytogenetic abnormality with prognostic significance)

Prognosis

- Median survival is two years.
- Patients are more likely to have serious infections or life-threatening bleeds than blastic transformation.
- MDS who progress to acute leukemia have a poor prognosis than that of de novo acute myeloid leukemia (response to chemotherapy is worse)
- International Prognostic Scoring System (IPPS)
 - The revised I (IPSS-R) score is calculated on the basis of five variables:
 - 1. Hemoglobin level
 - 2. Absolute neutrophil count
 - 3. Platelet count
 - 4. Percentage of bone marrow blasts
 - 5. Cytogenetic category

Management

- Supportive therapy.
 - including transfusions of the cells that are deficient (ie, red blood cells [RBCs], platelets), and treatment of infections are the main components of care.
 - As the vast majority are elderly patients with other medical conditions, excessive intervention is unwarranted (لا مبرر له).
 - Granulocyte-colony stimulating factor (G-CSF) and recombinant erythropoietin (r-Epo) can improve blood counts.
 - National Comprehensive Cancer Network (NCCN) guidelines recommend the use of erythropoiesis-stimulating agents (ESAs) for treatment of symptomatic anemia in patients in the R-IPSS very low risk, low risk, or intermediate risk category whose tumor lacks the 5q31 deletion and whose level of endogenous EPO is ≤500 mU/mL.
 - In cases of the presence of ringed sideroblasts or an absence of response, the addition of granulocyte colony-stimulating factor (G-CSF; filgrastim), 1–2 µg/kg 1–3 times per week should be considered.
- hypomethylating agent azacytidine, which has been shown to improve survival compared with either supportive or aggressive therapy and is approved for use in MDS by (FDA).
- Aggressive cytotoxic chemotherapy is generally reserved for treatment of transformation to acute myelogenous leukaemia (AML) in younger patients.

Leuco-erythroblastic anaemia

- leuco-erythroblastic anaemia (left-shifted granulocytic series and nucleated red blood cells)
- This can be seen with:
 - high bone marrow turnover, e.g. in severe haemolytic anaemia
 - (the reticulocyte count will be high),
 - > myelofibrosis and chronic myeloid leukaemia
 - (where there will be splenomegaly and the white cell and platelet count will usually be raised)
 - bone marrow invasion.
 - Often in bone marrow invasion the invading malignancy will already have been diagnosed previously.
 - The diagnosis requires a bone marrow trephine, which will usually show replacement of haematopoietic tissue with malignant cells.

Polycythaemia

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Types and causes

- · Relative causes
 - dehydration
 - > stress: Gaisbock syndrome
- Primary causes
 - polycythaemia rubra vera
- Secondary causes
 - > Erythropoietin-secreting tumours:
 - Renal cell carcinoma
 - Hepatocellular carcinoma
 - Haemangioblastoma
 - Uterine fibroids.
 - Chronic hypoxia:
 - COPD
 - Right-to-left cardiac shunts
 - Sleep apnoea
 - High altitude
 - Chronic carbon monoxide poisoning (including heavy smoking).

Features

- Symptoms of hyperviscosity syndrome, including:
 - dizziness
 - tinnitus
 - headaches
 - blurred vision, and
 - pruritus.
- Signs include:
 - Various ophthalmological changes (for example, dilated retinal veins)
 - Neurological findings,
 - Facial plethora ('ruddy' appearance).

	ЕРО	Expected plasma volume	Oxygen saturation	Underlying conditions
Relative (apparent) polycythemia (↑RBC mass due to ↓in plasma volume)	\leftrightarrow	\	\leftrightarrow	Severe dehydrationStress erythrocytosis
Appropriate absolute polycythemia (physiological †in RBC mass, secondary to conditions associated with increased stimulation of erythropoiesis due to reduced oxygen saturation)	1	\leftrightarrow	↓	High-altitude exposure Hypoxia: chronic pulmonary and cardiac disease
Inappropriate absolute polycythemia (non-physiological ↑ in RBC mass, secondary to conditions associated with autonomous production of EPO, renal diseases that affect the EPO secreting cells, and neoplasms).	$\uparrow \uparrow$	\leftrightarrow	\leftrightarrow	Paraneoplastic syndrome, especially with: Renal cell carcinoma (RCC) Hepatocellular carcinoma (HCC) Polycystic kidney disease (PKD)

- Absolute erythrocytosis, as opposed to apparent, is defined as an HCT greater than 0.60 in males and HCT greater than 0.56 in females.
- To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia:
 - > JAK2 mutation
 - JAK2 is a crucial tyrosine kinase which transmits the EPO signal to increase red cells production.
 - > Red cell mass studies
 - The discovery of the JAK2 mutation has made red cell mass a second-line investigation for patients with suspected JAK2-negative PRV.
 - In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

Management

- Venesection of patients who are symptomatic is the first line management of polycythaemia.
- The diagnostic workup and exclusion of secondary causes usually follows after initial treatment
 - patient with symptoms of <u>hyperviscosity</u> needs to be venesected <u>urgently</u> and an agreed <u>work-up can be performed later</u>.

Polycythaemia rubra vera (PRV)

Polycythaemia rubra vera is associated with a low ESR

Polycythaemia rubra vera - around 5-15% progress to myelofibrosis or AML

Polycythaemia rubra vera - JAK2 mutation

Definition

 Polycythaemia rubra vera (PRV) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets.

Aetiology

- a mutation in JAK2 is present in approximately 95% of patients with PRV and this has resulted in significant changes to the diagnostic criteria.
- occurs due to abnormal negative feedback of hematopoietic growth factor signaling.

Epidemiology

• peak incidence in the sixth decade

Pathophysiology

mutation in the JAK2 gene → ↑ tyrosine kinase activity → uncontrolled, EPO-independent proliferation of the myeloid cell lines → ↑ blood cell mass (erythrocytosis, thrombocytosis, and granulocytosis) → hyperviscosity + slow blood flow → ↑ risk of thrombosis and poor oxygenation.

Features

- hyperviscosity
- · pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet **function** NOT NUMBER)
- plethoric appearance
- hypertension in a third of patients
- low ESR
- Low EPO levels
 - > the strongest pointer towards primary polycythaemia
 - ➤ myeloproliferative → increased red blood cell production by the marrow → turns off endogenous EPO production →low EPO level.
- raised leukocyte alkaline phosphatase (ALP)
- Mild prolonged PT & PTT: this is related to the ratio of plasma and citrate. In the blue
 tubes that are used for coagulation tests the ratio is normally 1 citrate to 9 of whole blood. If
 there is less plasma due to the polycythaemia there will be excess citrate and this will
 prolong coagulation tests such as the APTT and prothrombin time.
- Others: hyperuricaemia, peptic ulceration.

Investigations

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- · renal and liver function tests
- If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- > abdominal ultrasound
- > serum erythropoietin level
- > bone marrow aspirate and trephine
- > cytogenetic analysis
- > erythroid burst-forming unit (BFU-E) culture

Diagnostic criteria

JAK2-positive PRV - diagnosis requires both criteria to be present

Criteria	Notes
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)
A2	Mutation in JAK2

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

Criteria	Notes
A1	Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women
A2	Absence of mutation in JAK2
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells
B1	Thrombocytosis (platelet count >450 * 10 ⁹ /l)
B2	Neutrophil leucocytosis (neutrophil count > 10 * 10 ⁹ /l in non-smokers; > 12.5*10 ⁹ /l in smokers)
В3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin

Management

- aspirin
- venesection:
 - first line treatment
 - \triangleright the target hematocrit value after performing phlebotomy is less than 45 %.
- Hydroxyurea:
 - the preferred cytoreductive agent used in high-risk patients.
 - > slight increased risk of secondary leukaemia
- phosphorus-32 therapy

- H2-receptor antagonists may be useful in relieving itching
 - this is somewhat surprising. Conventionally it is the H1 antagonists that tend to be used for pruritus in other settings.

Prognosis

- thrombotic events are a significant cause of morbidity and mortality
- 5-15% of patients progress to myelofibrosis
 - ➤ Pastest note → Transition from primary polycythaemia to myelofibrosis occurs in about 30% of patients, therefore, the probability of developing myelofibrosis is higher and thus more likely than acute leukaemia
- 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment)
 particularly if patients have been exposed to radioactive phosphorous treatment or busulfan therapy.
 - Progression to acute myeloid leukaemia is seen in around 5% of patients.

Mvelofibrosis

- Primary myelofibrosis is a disorder in which normal bone marrow tissue is gradually replaced with a fibrous scar-like material.
- Over time this leads to progressive bone marrow failure.
- Most commonly seen in older adults (5th/6th decade)
- It is almost always accompanied by significant splenomegaly and is JAK2 mutation-positive in about 50% of cases.
- · fatigue, splenomegaly and teardrop cells

Complications

- Portal hypertension
 - > occurs in 7% of patients with primary myelofibrosis
 - may be related to increased portal flow resulting from marked splenomegaly and to intrahepatic obstruction resulting from thrombotic obliteration of small portal veins.
 - This may result in variceal bleeding or ascites.
 - ➤ Hepatic or portal vein thrombosis may occur.
 - > Symptomatic portal hypertension is managed by splenectomy, with or without the creation of a portosystemic shunt.
- Peripheral blood smear
 - > tear-drop RBC
 - membrane is disrupted when RBC passed through fibrosis to leave bone marrow
 - nucleated RBCs
 - band granulocytes

Treatment

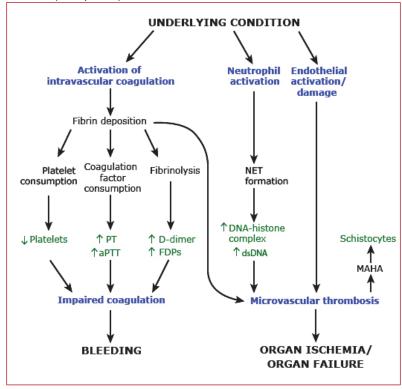
- It is generally incurable,
- although bone marrow transplantation and JAK2 inhibitors have a role in younger patients.

Disseminated intravascular coagulation (DIC)

Pathophysiology

- (DIC) is characterized by:
 - ➤ systemic activation of blood coagulation → deposition of fibrin → microvascular thrombi in various organs → multiple organ dysfunction syndrome (MODS).
 - ➤ ongoing activation of coagulation → consumption of coagulation proteins and platelets → may induce severe bleeding

Pathogenesis of DIC (2020 UpToDate)



NET: neutrophil extracellular trap; **PT**: prothrombin time; **aPTT**: activated partial thromboplastin time; **FDPs**: fibrin degradation products; **dsDNA**: double-stranded DNA; **MAHA**: microangiopathic hemolytic anemia.

Epidemiology

· present in 1% of hospitalized patients.

Common Causes

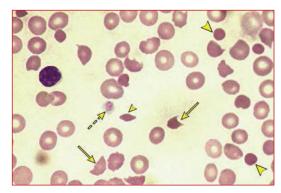
- · Sepsis and severe infection (most commonly)
- Trauma (neurotrauma)
- Organ destruction (eg, pancreatitis)
- Malignancy (solid and lymphoproliferative/myeloproliferative malignancies)
- acute hemolytic transfusion reaction.
- Obstetric complications:
 - Amniotic fluid embolism
 - abruptio placentae
 - (HELLP) syndrome : triad of:
 - 1. Hemolysis,
 - 2. Elevated Liver enzymes,
 - 3. Low Platelets
 - eclampsia

Diagnosis

- CBC
 - Thrombocytopenia (low Platelet count)
- · Coagulation profile
 - prolonged PT and aPTT
 - low plasma fibrinogen
- D-dimers
 - produced by the action of plasmin on cross-linked fibrin
 - > These tests reflect the microangiopathy of DIC
 - > sensitive, specific, and efficient in the diagnosis of DIC
- Fibrin degradation products (FDP)
 - ➤ Increased levels of FDP occur in a variety of conditions in which clot formation and lysis occur.
 - > sensitive, specific, and efficient in the diagnosis of DIC

the combination of the D-dimer and the FDP assay provides the most rapid and specific diagnosis of DIC.

- · Peripheral smear
 - > microangiopathic changes on peripheral blood smear
 - The presence of schistocytes, or red cell fragments, is a frequent but nonspecific



Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

Treatment

- Fibrinogen replacement infusion (cryoprecipitate) is the appropriate first choice
- Platelet transfusion is recommended if the count is less than 50 ×10⁹/L.
- When bleeding is the major problem, the aim is to:
 - maintain the prothrombin and activated thromboplastin time at a ratio of 1.5 times of the control
 - maintain the fibrinogen level above 1 g/L.

Thrombocytopenia

Causes of thrombocytopenia:

- ❖ ↓production (bone marrow infiltration, suppression, or fibrosis),
- ↑ destruction (DIC, ITP, and TTP/HUS),
- dilution
- sequestration due to splenomegaly.

Causes of severe thrombocytopenia

- ITP
- DIC
- TTP
- haematological malignancy

Causes of moderate thrombocytopenia

- heparin induced thrombocytopenia (HIT)
- drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides)
- alcohol
- liver disease
- hypersplenism
- viral infection (EBV, HIV, hepatitis)
- pregnancy
- SLE/antiphospholipid syndrome
- vitamin B12 deficiency

Gestational thrombocytopaenia

- · very common.
- Most importantly, the patient should be closely monitored from the present time until she delivers
- The platelet count is very mildly reduced
- · no specific intervention
- Steroids may only need to be considered if the platelet count is persistently less than 30 within the last 2 weeks of pregnancy.
- Steroids may be considered in the last couple of weeks of pregnancy to raise the platelet count temporarily so that a caesarean section or epidural anaesthesia may be undertaken safely. This may well be combined with intravenous immunoglobulin

immune thrombocytopenia

- the patient is well.
- There is post viral illness with quite marked thrombocytopenia but other full blood count (FBC) parameters are normal.
- The diagnosis is one of exclusion,
- The most important investigation is a blood film. Although not diagnostic, this will
 confirm the FBC findings and also exclude more sinister pathology such as
 leukaemia.
- in the absence of major bleeding, management would be observation, as it can resolve spontaneously.

Safety for different procedures when thrombocytopenic:

• In general, a platelet count of 10-20 ×10⁹ /L is safe for most procedures. The exceptions to this are major surgery and procedures involving the CNS and eyes. In the latter cases, the platelet count should be above 50 ×10⁹/L.

Thrombocytosis

Definition

- Thrombocytosis is an abnormally high platelet count, usually ≥450 × 10⁹/L
- Thrombopoietin is the key hormone in the regulation of megakaryocyte differentiation.

Causes

- reactive: platelets are an acute phase reactant platelet count can increase in response to stress such as a severe infection or surgery
 - > The most common cause of thrombocytosis is a reactive thrombocytosis.
 - May occur as a response to exercise
 - Secondary thrombocytosis does not place the patient at risk for haemostatic or cardiovascular events.
- iron deficiency
- Malignancy
 - secondary cause for thrombocytosis is crucial to exclude before considering a diagnosis of a myeloproliferative disorder.
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
 - adequate iron stores are requisite diagnostic criteria (WHO) for essential thrombocytosis.
- hyposplenism

Essential thrombocytosis (ET):

Definition

- Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis.
- Megakaryocyte proliferation results in an overproduction of platelets, in the absence of any identifiable cause.

Epidemiology

- usually affects older people between the ages of 50 and 70 years
- · occurs equally in both males and females.

Features

- asymptomatic (25-33%)
- tingling or burning in the hands and feet, headache, visual problems, weakness and dizziness.
 - burning sensation in the hands is a characteristic symptom
 - Erythromelalgia
 - burning pain, warmth, and redness of the extremities
 - The pain increases with exposure to heat and improves with cold
 - These symptoms result from excessive numbers of platelets causing blockages in small or large blood vessels in different parts of the body.
- Other symptoms include sweating, low-grade fever, and pruritus.
- Splenomegaly (40-50%)
- Hepatomegaly (20%)
- both thrombosis and haemorrhage can be seen

Investigations

- Complete blood cell count (CBC)
 - platelet count > 600 * 10⁹/I
 - Around 30% will also have a mildly raised RBC and / or WBC.
 - A red blood cell (RBC) mass study helps to exclude polycythemia vera. The RBC mass is elevated in polycythemia vera, but is normal in essential thrombocytosis.

- Genetic studies
 - > The majority of patients have mutations in one of three genes:
 - 1. Janus kinase 2 (JAK2),
 - **50-60%** of patients.
 - 2. calreticulin (CALR),
 - ❖ found in 25%
 - 3. myeloproliferative leukemia virus oncogene (MPL).
 - ❖ about 3-5% of cases.
 - MPL codes for the thrombopoietin receptor protein, which promotes the growth and proliferation of megakaryocytes.
 - The mutations result in constitutive activation of the thrombopoietin receptor protein.
 - Rare cases involve mutations in the thrombopoietin gene (*THPO*),
 - associated with autosomal dominant hereditary thrombocytosis
- · Bone marrow examination
 - → ↑ bone marrow cellularity (found in 90%)
 - Megakaryocytic hyperplasia is common
 - ➤ Bone marrow reticulin is usually increased, but collagen fibrosis is uncommon
- Elevation of C-reactive protein (CRP), fibrinogen, and interleukin 6 levels suggests secondary thrombocytosis, because those are acute-phase reactants
- Vitamin B-12 levels are increased in 25% of patients
- Uric acid levels are elevated in 25% of patients

Diagnosis

- British guidelines propose the following five criteria for diagnosis of essential thrombocytosis:
 - 1. Sustained platelet count ≥450 × 10⁹/L
 - Presence of an acquired pathogenetic mutation (eg, in the JAK2, CALR or MPL genes)
 - 3. No other myeloid malignancy, especially polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome
 - 4. No reactive cause for thrombocytosis and normal iron stores
 - 5. Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm; reticulin is generally not increased (grades 0–2/4 or grade 0/3)
 - ➤ Diagnosis requires the presence of criteria 1–3 or criterion 1 plus criteria 3–5.

Adverse prognostic markers for essential thrombocythaemia (ET):

- Age above 60
- · Symptomatology particularly thrombosis and
- Platelet count above 1500.
- · Previous thrombosis
- Obesity
- Cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia
- Markers of hypercoagulability such as factor V Leiden and antiphospholipid antibodies [4]
- JAK2 mutation

Management

Essential thrombocythaemia + high-risk of thrombosis → Aspirin + hydroxycarbamide

- low risk → observation only
- high-risk of thrombosis (eg, age >60, history of thrombosis, or platelet counts >1500).
 - > hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
 - first-line treatment
 - > interferon-α is also used in younger patients
 - Interferon alfa is a biologic response modifier.
 - used as second line in older patient
 - Interferon alfa is not known to be teratogenic and does not cross the placenta, perhaps making it <u>safe for use during pregnancy</u>.
 - Italian guidelines recommend interferon alfa as a first-line platelet-lowering therapy for patients younger than 40 years
 - > low-dose aspirin may be used to reduce the thrombotic risk
 - low-dose aspirin may be useful in treating patients with symptoms of microvascular occlusion (eg, erythromelalgia).
 - Patients with the JAK2 mutation or cardiovascular risk factors can be treated with daily low-dose aspirin
 - Extreme thrombocytosis may promote the abnormal adsorption of large von Willebrand factor (VWF) multimers.
 - These patients should be screened for the presence of acquired von Willebrand disease (VWD).
 - if ristocetin cofactor level (Functional von Willebrand Factor) is at least 30% in absence of other high-risk factors; Low-dose aspirin therapy (eq. ≤100 mg/day) is acceptable
 - if it is less than 30%, all aspirin should be avoided.
- Plateletpheresis
 - If platelet is very high with symptoms of clotting or bleeding

Prognosis

- extremely good in ET with survival of over two decades expected.
- The risk of transforming to acute myeloid leukaemia is relatively low (<1%).

Thrombotic thrombocytopenic purpura (TTP)

(TTP) is classically characterised as a **pentad of**: thrombocytopenia, microvascular haemolysis, fluctuating neurological signs, renal impairment and fever.

HUS or TTP? Neuro signs and purpura point towards TTP

TTP - plasma exchange is first-line

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)

- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of ADAMTS13 (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor
- The primary event that occurs appears to be endothelial damage, which then leads to →
 thrombus formation, → end organ damage (eg brain and kidneys) and platelet
 consumption
- overlaps with haemolytic uraemic syndrome (HUS)

Causes

- post-infection e.g. urinary, gastrointestinal (Escherichia coli 0157 subtype)
- pregnancy

drugs:

- > ciclosporin,
- oral contraceptive pill,
- > penicillin, metronidazole
- antiplatelets: clopidogrel or ticlodipine (< 1%),</p>
- acyclovir,
- > FK506.
- Penicillamine
- sulphonamides
- tumours
- SLE
- HIV

Features

- rare, typically adult females
- fever
- fluctuating neuro signs (microemboli)
- microangiopathic haemolytic anaemia
- renal failure
- thrombocytopenia
- Which investigation will be most useful to establish the diagnosis?
 - Peripheral blood film
 - The peripheral blood film reveals fragmented RBCs (schistocytes, eg, spherocytes, segmented RBCs, burr cells, or helmet cells).

Management

- · no antibiotics may worsen outcome
- plasma exchange is the treatment of choice
 - > TTP has an untreated mortality of up to 90% and therefore rapid plasma exchange (PEX) may be a life saving intervention.
- steroids, immunosuppressants
 - Intravenous methylprednisolone is indicated after treatment with PEX has been completed.
- Vincristine
- Platelet transfusion in TTP is only indicated if there is an on-going life-threatening bleed.
- There is no current role for intravenous immunoglobulin in the routine management of TTP, however there have been reports of its successful use in PEX- and steroid-refractory cases.

Prognosis

• In adults, the mortality rate 20-50%

January 2013 exam: H/O confusion + fever + ↓Platelets 65 , ↑Urea 23, ↑Creatinine 366.What is the most likely diagnosis?

→ Thrombotic thrombocytopenic purpura

Von Willebrand's disease

The combination of a petechial skin rash combined with a slightly elevated APTT and reduced factor VIII activity make Von Willebrand's disease the most likely diagnosis

Desmopressiin - induces release of von Willebrand's factor from endothelial cells

Overview

- Von Willebrand's disease is the most common inherited bleeding disorder.
- The majority of cases are inherited in an autosomal dominant fashion
 - if both parents have the disease, then three-quarters of their offspring will have the disease, assuming they are both heterozygotes.
 - In an autosomal dominant condition, there is no carrier state.
- characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemoarthroses and muscle haematomas are rare
- Symptoms are exacerbated by medications that inhibit platelet function, such as aspirin and other NSAIDs.

Role of von Willebrand factor

- large glycoprotein which forms massive multimers
- Von Willebrand factor is a coagulation protein that binds to collagen and to the Gplb platelet receptor during platelet adhesion.
 - > promotes platelet <u>adhesion</u> to damaged endothelium
- carrier molecule for factor VIII
- Factor VIII circulates bound to von Willebrand factor (vWF), which <u>protects factor VIII</u> from degradation.
 - Decreased vWF (in part) prolongs the PTT by leading to decreased factor VIII.
 - In people with hemophilia, strategies to increase circulating levels of factor VIII include maximizing vWF levels.
 - > increases vWF secretion (leading to increased functional levels of factor VIII).
 - > Even in hemophilia A, there is still a small amount of normal factor VIII (<5%).
- The intrinsic coagulation pathway is defective in you Willebrand disease.

Types

- type 1: partial reduction in vWF (80% of patients)
 - the most common form
 - > patients have up to a 50% reduction in von Willebrand factor (vWF).
 - Autosomal dominant with variable penetrance
 - Many are asymptomatic and are only diagnosed following an episode of bleeding associated with a dental extraction or minor surgery.
- type 2: abnormal form of vWF
- type 3: total lack of vWF (autosomal recessive) (most severe form)

Investigation

- prolonged bleeding time (due to impaired platelet adhesion and aggregation)
 - The bleeding time would be a good <u>screening test</u> but it will not give a quantitative measurement of bleeding tendency in type I vWBD
 - > neither sensitive nor specific
 - platelet function analyser (PFA100), have better testing characteristics than the bleeding time
- APTT may be prolonged (due to reduced circulating factor VIII).
- factor VIII levels may be moderately reduced

- ➤ the most useful test to <u>assess bleeding tendency</u> in Von Willebrand's disease
 ? → Plasma factor VIII activity
- vWB antigen and activity (Ristocetin cofactor assay) (RICOF)
 - > The most useful test in practice is to do the vWB antigen and activity (RICOF), but you would also do FVIIIc as this is also low in vWD.
- In type I vWD the prothrombin time (PT) and Platelet count will be normal.
- · defective platelet aggregation with ristocetin

Management

- · tranexamic acid for mild bleeding
- desmopressin (DDAVP):
 - raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells
 - DDAVP is the initial treatment of choice for patients with VWD type 1.
 - Other therapies such as factor VIII concentrates containing VWF are not usually required.
- · factor VIII concentrate
- In minor trauma,
 - desmopressin (DDAVP) can be used to increase the concentration of VWF.
 - > The choice of treatment for a mild vWB facing a more invasive procedure would be DDAVP, providing there is no contraindication.
 - > vWB factor concentrate would be reserved as second line treatment to DDAVP.
- · for major surgery,
 - factor VIII concentrate is used to increase the concentration of vWF.
 - The most commonly used is Humate-P.
 - Purified or recombinant preparations are avoided since they contain only small concentrations of vWF.
 - In cases of severe vWD or prior to major surgery, the product of choice is intermediate purity (vWF rich) factor VIII, which contains the highest concentration of von Willebrand factor.
- · for Women with menorrhagia:
 - Oral contraceptives (the Pill) raise the level of von Willebrand factor in the blood for women with Type 1 VWD.

Haemophilia

Definitions

- Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX
 - ➤ Hemophilia A (factor VIII): ~ 80% of cases
 - ➤ Hemophilia B (factor IX): ~ 20% of cases

Etiology

- X-linked recessive disorder
 - > Occurs almost exclusively in males due to an X-linked pattern of inheritance.
 - typically skips generations
 - A carrier mother has a 50% chance of passing down the disease to her sons and a 50% chance of passing down the carrier gene to her daughters.
- Up to 30% of patients have no family history of the condition.

Pathophysiology

- The pathological problem in both haemophilia A and haemophilia B is the inability to form a functional tenase complex to activate factor X to factor Xa
- The intrinsic coagulation pathway is defective in hemophilia.

Features

- typically present initially with easy bruising secondary to minimal trauma,
- · haemoarthroses, haematomas

- Musculoskeletal bleeding is the most common type of haemorrhage.
- · prolonged bleeding after surgery or trauma,

Severity	Clinical signs	Factor VIII or IX activity
Physiologic condition	None	≥ 50%
Mild hemophilia	Hematomas following severe trauma	> 5% to < 50%
Moderate hemophilia	Hematomas following mild trauma	≥ 1% to 5%
Severe hemophilia	Spontaneous hematomas	< 1%

Petechial bleeding is a common sign of platelet disorders, NOT coagulation disorders such as hemophilia

Blood tests

- prolonged APTT
- mixing study
 - requested if the aPTT is prolonged.
 - > The patient's plasma is mixed with normal plasma and the aPTT repeated.
 - Correction of aPTT with mixing study suggests coagulation factor deficiency.
- plasma factor VIII and IX assay
- bleeding time, thrombin time, prothrombin time normal

Although female carriers of the haemophilia gene do not normally suffer from increased bleeding risk, APTT may be prolonged.

Treatment

- · factor VIII or IX replacement.
- · Side effects:
 - Up to 10-15% of patients with haemophilia A develop <u>antibodies to factor VIII</u> <u>treatment</u>

Methemoglobinemia

Methemoglobin

- hemoglobin is oxidized to the ferric (Fe³⁺)
- ■ affinity for O₂
- ↑ affinity for cyanide (CN⁻)
 - > CN poisoning treated with methemoglobin
- Methemoglobin (met-Hb) results from the presence of iron in the ferric form (Fe³⁺) instead
 of the usual ferrous form (Fe²⁺).
- met-Hb cannot carry oxygen
- met-Hb is a naturally occurring oxidized metabolite of hemoglobin, and physiologic levels (< 1%) are normal.
- Methemoglobinemia (congenital or acquired) occurs when (RBCs) contain methemoglobin at levels higher than 1%.
- Acquired methemoglobinemia is considerably more common than congenital forms.
- The low level of methemoglobin is maintained through 2 important mechanisms.

- 1. the hexose-monophosphate shunt pathway within the erythrocyte. Through this pathway, oxidizing agents are reduced by glutathione.
- 2. The second and more important mechanism involves two enzyme systems:
 - diaphorase I: requires nicotinamide adenine dinucleotide (NADH)
 - the major enzymatic system (This enzyme system is responsible for the removal of 95-99% of the methemoglobin that is produced under normal circumstances.)
 - Cytochrome b5 reductase plays a major role in this process by transferring electrons from NADH to methemoglobin, an action that results in the reduction of methemoglobin to hemoglobin.
 - diaphorase II: requires nicotinamide adenine dinucleotide phosphate (NADPH).
 - plays only a minor role in the removal of methemoglobin.
 - This enzyme system utilizes glutathione production and glucose-6phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin.
 - Play a more important role in methemoglobin regulation in patients with cytochrome b5 reductase deficiencies.
 - can be accelerated by exogenous cofactors such as methylene blue

Effect of Methemoglobin:

- does not bind oxygen, thus leading to a functional <u>anemia</u>.
- causes a <u>left shift of the oxygen-hemoglobin dissociation curve</u>, resulting in decreased release of oxygen to the tissues.
 - > Normal people generate met-Hb but in very low levels in the range of 0.5% to 3%.
 - ➤ should be suspected when the oxygen saturation as measured by pulse oximetry is significantly different (lower) from the oxygen saturation calculated from arterial blood gas analysis (saturation gap). (low SpO₂ with normal PaO₂ and SaO₂(on ABG)
- presence of <u>anemia and cyanosis</u> despite oxygen treatment results from both of these effects.

Causes

- congenital (secondary to a deficiency in methemoglobinemia reductase)
- acquired
 - Dapsone
 - local anesthetics (topical and injectable)
 - nitrates
 - amyl nitrite
 - aniline dyes
 - The presence of methemoglobin may also be a marker and predictor of sepsis, resulting from release of excessive amounts of nitrous oxide (NO)
 - ➤ patients with low catalase activity (inherited or acquired) treated with rasburicase for tumor lysis syndrome → formation of hydrogen peroxide → methemoglobinemia
 - Some authors have suggested that catalase activity be measured before rasburicase therapy is initiated in this setting.

Drugs that cause methaemoglobinaemia include:

- Phenacetin
- Sulphonamides
- Dapsone
- Primaguine
- Lidocaine
- Procaine
- Benzocaine.

Congenital (hereditary) Methemoglobinemia

- · autosomal recessive
- two forms of congenital cytochrome b5 reductase (b5R) deficiency exist:

type Ib5R deficiency	type IIb5R
more common	less common
cytochrome b5 reductase is absent only in RBCs	cytochrome b5 reductase is deficient in all cells, not just RBCs.
Homozygotes appear cyanotic but usually are otherwise asymptomatic.	associated with several other medical problems, including mental retardation, microcephaly, and
Heterozygotes may develop acute, symptomatic	other neurologic complications.
methemoglobinemia after exposure to certain drugs or toxins.	Life expectancy is severely compromised, and patients usually die at a very young age.
Methemoglobin levels typically range from 10% to 35%.	
Life expectancy is not influenced	

presence of abnormal hemoglobins (hemoglobin M [Hb M])

- autosomal dominant
- in most of these hemoglobins, tyrosine replaces the histidine residue, which binds heme to globin.
- This replacement displaces the heme moiety and permits oxidation of the iron to the ferric state.
- Hb M is more resistant to reduction by the methemoglobin reduction enzymes
- Patients with Hb M appear cyanotic but are otherwise generally asymptomatic.

Feature (are proportional to the methemoglobin level):

Classical presentation includes cyanosis with chocolate-colored blood

- 3-15% Slight discoloration (eg, pale, gray, blue) of the skin and blood color changes (brown or chocolate color).
 - Discoloration of the skin and blood is the most striking physical finding.
 - > Fatigue, flu-like symptoms, and headaches may be the only manifestations in the initial phase.
- 15-20% Cyanosis, though patients may be relatively asymptomatic
 - cyanosis is usually the first presenting symptom.
- 25-50% Headache, dyspnea, lightheadedness (even syncope), weakness, confusion, palpitations, chest pain
- 50-70% Abnormal cardiac rhythms; altered mental status, delirium, seizures, coma; profound acidosis
- >70% Usually, death

Treatment:

- Methylene blue:
 - > the first line treatment
 - contraindicated in G6PD deficiency and ineffective with hemoglobin M.
 - reduction of met-Hb by methylene blue is dependent upon NADPH generated by G6PD.
 - methylene blue has an oxidant potential → hemolysis in G6PD deficient.
- Second line treatment: when methylene blue therapy is ineffective or contraindicated
 - Exchange transfusion: for patients who do not respond to methylene blue or G6PD-deficient individuals who are severely symptomatic
 - > Hyperbaric oxygen treatment: another option
 - IV hydration and bicarbonate (for metabolic acidosis)

Cyanosis without hypoxia

- Persistent cyanosis without hypoxia (a normal Pao2) suggests a diagnosis of methaemoglobinaemia or sulfhaemoglobinaemia.
- In a cyanosed patient the amount of reduced haemoglobin in the blood is at least 5 g/dl
- The blue colour of the skin and mucous membranes is due to hypoxia and not hypercapnia. Hypoxia should be corrected by oxygen therapy
- What is the possible cause of Desaturation on SaO₂ (using an oximeter) in spite of normal PaO₂?
 - > Methaemoglobinaemia
 - accumulation of reversibly oxidised methaemoglobin causing reduced oxygen affinity of the Hb molecule with consequent cyanosis.
 - It can occur due to:
 - an inherited condition or
 - as a consequence of drugs such as nitrites.

Heparin

- can be given as either:
 - > unfractionated, intravenous heparin, or
 - low molecular weight heparin (LMWH), given subcutaneously.
- Heparins generally act by activating antithrombin III.
- Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa.
- LMWH however only ↑ the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

	Standard Heparin	(LMWH)
administration	Intravenous	Subcutaneous
Action duration	short	long
Mechanism of action	Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa	Activates antithrombin III. Forms a complex that inhibits factor Xa
Side-effects	Bleeding HIT Osteoporosis	Bleeding Lower risk of HIT and osteoporosis
Monitoring	Activated partial thromboplastin time (APTT)	Anti-Factor Xa (although routine monitoring is not required)
Notes	Useful in situations where there is a↑ risk of bleeding as anticoagulation can be terminated rapidly	Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

Heparin-induced thrombocytopaenia (HIT)

- Types
 - 1. Type 1 HIT
 - non-immune mediated reaction
 - due to a direct effect of the drug on platelets.
 - occur soon after the initial administration of heparin (within two days)
 - self-limiting condition and the platelet count will normalise with continued heparin administration.
 - 2. Type 2 HIT
 - immune mediated condition
 - mechanism:
 - IgG antibodies against heparin bound to platelet factor 4 (PF4).
 - Antibody-heparin-PF4 complex will be eliminated by the immune system (→ thrombocytopenia), and activates platelets → thrombosis
 - It is a prothrombotic condition despite being associated with low platelets.
 - typically arises 4 to 10 days after starting heparin therapy.
 - Patients may develop both venous and arterial thromboses,
 - low platelet counts and mild abnormalities of coagulation.
 - The D-dimer level is raised due to widespread thrombus formation.
- Features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- Patients with (HIT), particularly those with associated thrombosis, often have evidence of increased thrombin generation that can lead to consumption of protein C.
 - ➤ If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis.
 - > To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor, or fondaparinux, until the platelet count returns to normal levels.
- **Diagnosis**: HIT is confirmed by:
 - > HIT antibody
 - > serotonin-release assay (SRA).
- Treatment
 - > options include alternative anticoagulants such as lepirudin and danaparoid
 - Argatroban is not cleared via the kidneys; therefore, this drug is safer than lepirudin/fondaparinux for HIT patients with renal insufficiency.
 - > Lepirudin is a direct thrombin inhibitor, which is cleared by kidneys exclusively, and is contraindicated in renal insufficiency.
 - ➤ Fondaparinux can be used in HIT as it does not bind to platelets, but it is contraindicated in renal insufficiency.

Heparin-induced hyperkalaemia

• Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose

- Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.
- The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration.
 - > If protamine is given within eight hours of the LMWH then a maximum neutralising

- ➤ If more **than eight hours** have passed since the dose of LMWH was given, administer **0.5 mg** protamine per 100 units (or 1 mg) of LMWH given.
- Protamine is administered by slow IV infusion (over 10 minutes) to avoid a hypotensive reaction.
- Protamine requires a high level of caution when being prescribed and administered.

Heparin resistance

- Heparin resistance is seen in up to 22% of patients undergoing cardiopulmonary bypass surgery.
- Several mechanisms resulting in heparin resistance have been identified, including:
 - > antithrombin deficiency.
 - > increased heparin clearance,
 - elevated heparin-binding proteins,
 - and elevated factor VIII and fibrinogen levels.
- For cardiopulmonary bypass in particular, rapid neutralisation of thrombin is required. In
 order for heparin to be successful in this, it requires antithrombin III which is an alpha2globulin. It is therefore thought that antitthrombin III deficiency is the underlying problem
 which is seen in patients resistant to heparin during cardiopulmonary bypass.
- Heparin and thyroid function test
 - ➤ Heparin is having an "in vitro" effect on thyroxine (T4) levels.
 - > IV heparin interferes with the thyroid function tests assay on occasions displacing bound thyroid hormone.
 - Normal TSH + high T3 and T4

Heparin and delivery

- Women who are anticoagulated with heparin until the onset of labor generally experience vaginal delivery with no greater blood loss than non-anticoagulated gravidas.
- However, Cesarean delivery in heparinized patients is accompanied by a significantly greater blood loss than would otherwise be anticipated.
- If preterm labor develops in a patient receiving heparin, only the mother is anticoagulated, and protamine sulfate can be used to reverse maternal heparinization.

What is the best way to monitor rivaroxaban compliance?

→ Prothrombin time (PT)

Novel oral anticoagulants (NOACs)

The table below summaries the three NOACs: dabigatran, rivaroxaban and apixaban.

	Dabigatran	Rivaroxaban	Apixaban
UK brand name	Pradaxa	Xarelto	Eliquis
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Route	Oral	Oral	Oral
Excretion	Majority renal	Majority liver	Majority faecal
NICE indications	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*	Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF*

*NICE stipulate that certain other risk factors should be present. These are complicated and differ between the NOACs but generally require one of the following to be present:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- heart failure

	Dabigatran	Rivaroxaban	Apix aban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Route	Oral	Oral	Oral
Excretion	Majority renal	Majority liver	Majority faecal

Dabigatran

Stop dabigatran two days before polypectomy

- Mode of action: Dabigatran is a direct thrombin inhibitor with a rapid onset of action.
- It is administered as a prodrug
 - ➤ The prodrug dabigatran etexilate is rapidly converted by tissue esterases to dabigatran.
- it is predominately (80%) excreted by the kidneys.
- The anticoagulant effect starts within minutes of oral ingestion and peaks after 2-3 hours.
- Advantage of dabigatran:
 - ➤ due to its short half-life, a patient's coagulation status will normalize more rapidly than that of a patient treated with warfarin in almost all cases.
 - > No need for routine monitoring
- · Disadvantage of dabigatran
 - Dabigatran is not recommended in patients with prosthetic heart valves because their safety and efficacy have not established.
 - The rates of thromboembolism are higher for valves in the mitral compared with those in the aortic position.
 - caged-ball valves are the most thrombogenic followed by tilting-disk and bi-leaflet valves.
 - ➤ more thromboembolic events (e.g., valve thrombosis, stroke, TIA, and myocardial infarction) were observed with dabigatran than with warfarin;
 - excessive major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) was observed with dabigatran, compared with warfarin.
- Monitoring of the anticoagulant effects of dabigatran
 - In general, "routine" monitoring is not required in most cases.
 - ➤ However, in some clinical situations a clinician may wish to determine the degree to which dabigatran is reducing the coagulant potential of the blood; e.g., if a patient taking dabigatran requires emergency surgery, has an intracranial or major systemic bleed, or is being considered for thrombolysis due to an ischemic stroke.
 - > The thrombin time (TT) and ecarin clotting time are considered the most accurate measures of dabigatran's anticoagulant effect.
 - ➤ The aPTT and, if available, the thrombin time (TT) should be used to measure the anticoagulant effect of dabigatran,
 - INR and PT tests are unreliable
- Effect of dabigatran on procedural bleeding risk
 - Dabigatran should be discontinued 1 to 2 days (creatinine clearance ≥ 50 mL/min) or 3 to 5 days (creatinine clearance <50 mL/min) before invasive or surgical procedures.</p>
 - ➤ Clinicians may want to consider "longer" periods of discontinuation for patients undergoing major surgery in which bleeding could have serious consequences (e.g.,

- cardiac, neurosurgery, major abdominal or pelvic, spinal puncture, or placement of a spinal or epidural catheter or port).
- ➤ If surgery is urgent and cannot be delayed, there is an increased risk of bleeding; patients with a normal aPTT appear to have a low risk of serious bleeding.
- conversion from warfarin to dabigatran (eg: patient had difficulty attending for regular INR)
 - ➤ if a patient is taking warfarin with a therapeutic INR, it is recommended to : Stop warfarin, perform daily INR, start dabigatran when INR falls below 2.0
 - ➤ The anticoagulant effect of dabigatran starts minutes after its oral administration and peaks after 2-3 hours.
- Contraindications
 - Dabigatran is contraindicated if eGFR <30ml/min.</p>
 - ➤ Rivaroxaban, a direct inhibitor of activated factor X, is contraindicated if eGFR <15 and needs dose adjustment if eGFR 15–29 mL/minute.

Ecarin clotting time is prolonged by direct thrombin inhibitors such as dabigatran.

Treatment with aspirin, warfarin or heparins does not affect Ecarin clotting time.

Idarucizumab reverses dabigatran

Warfarin

Warfarin - clotting factors affected mnemonic - 1972 (10, 9, 7, 2)

P450 inhibitors ↑ INR

INR also ↑ by ABX that kill intestinal flora by ↓ Vit K absorption

Dentistry in warfarinised patients - check INR 72 hours before procedure, proceed if INR < 4.0

Warfarin action → inhibition of vitamin K epoxide reductase

- Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of clotting factor II, VII, IX and X (mnemonic = 1972) and protein C. (warfarin → reduces protein C levels in the blood)
- Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues which inhibits the carboxylation activity of the glutamyl carboxylase.
- The half-life of warfarin is approximately 44 h

Indications

- venous thromboembolism: target INR = 2.5, if recurrent 3.5
- atrial fibrillation, target INR = 2.5

mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

Side-effects

- haemorrhage
- teratogenic, although can be used in breast-feeding mothers
 - ➤ the most common teratogenic effect is → Nasal hypoplasia
- skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- purple toes

Contraindications

- Warfarin is generally avoided in pregnancy.
 - In the first trimester it is associated with an increased risk of miscarriage, and teratogenic side effects which include chondrodysplasia patellae, asplenia and diaphragmatic herniae.
 - > In the second and third trimester it is associated with retroplacental and intracerebral foetal haemorrhage, as well as foetal microcephaly, optic atrophy and developmental delay.

Monitoring

- Patients on warfarin are monitored using the INR (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time.
- Warfarin has a long half-life and achieving a stable INR may take several days.

Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, Clarithromycin, ciprofloxacin
 - > Clarithromycin increase INR more than ciprofloxacin
 - Clarithromycin is metabolised by CYP3A4 and is an inhibitor, meaning that it does affect INR to a limited extent, leading to an increase.
 - Ciprofloxacin is a moderate inhibitor of CYP1A2; some effect is expected on INR, but not as great as that for clarithromycin.
- · cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

Interaction

- Lipid-lowering agents
 - ➤ Simvastatin, rosuvastatin and fibrate → potentiate the anticoagulant effects of
 - > Atorvastatin and pravastatinare least likely to interfere with warfarin
 - > Cholestyramine (a cholesterol-binding resin) is known to reduce the anticoagulant action of warfarin
 - Cholestyramine reduces absorption of a number of drugs including warfarin.
- cranberry juice →(↑↑warfarin effect → ↑↑ INR). The cause is thought to be bioflavonoids contained in the cranberry juice, which block cytochrome-P450-related warfarin metabolism (CYP2C9)
- Paracetamol given in repeated doses may lead to an enhanced response to warfarin and therefore an increased INR
- Commonly used drugs that may lead to an increased INR include cephalosporins, azathioprine, cimetidine, metronidazole and testosterone derivatives
- Diazepam is a p450 enzyme inducer and is therefore likely to reduce INR

- the concurrent use of clopidogrel with warfarin increases the bleeding risk.
- Co-enzyme Q10 is similar to vitamin K and reduces warfarin's anticoagulant effect
 (warfarin exerts its anticoagulant effect though inhibition of the synthesis of vitamin K
 dependent clotting factors).

Warfarin: management of high INR

A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding.

Situation	Management
Major bleeding	 Stop warfarin Give intravenous vitamin K 5mg Prothrombin complex concentrate - if not available then FFP
INR > 8.0 Minor bleeding	 Stop warfarin Give intravenous vitamin K 1-3mg Repeat dose of vitamin K if INR still too high after 24 hours Restart warfarin when INR < 5.0
INR > 8.0 No bleeding	 Stop warfarin Give vitamin K 1-5mg by mouth, using the intravenous preparation orally Repeat dose of vitamin K if INR still too high after 24 hours Restart when INR < 5.0
INR 5.0-8.0 Minor bleeding	 Stop warfarin Give intravenous vitamin K 1-3mg Restart when INR < 5.0
INR 5.0-8.0 No bleeding	 Withhold 1 or 2 doses of warfarin Reduce subsequent maintenance dose

^{*}as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage

Prothrombin concentrates are products of choice for warfarin reversal in the setting of active bleeding and a markedly raised INR.

management of mother and neonate if preterm labor develops in a patient on warfarin

- The management is difficult if preterm labor develops in a patient on warfarin, because both the mother and the fetus are anticoagulated.
- the best management to prevent fetal/neonatal hemorrhage → Give fresh frozen plasma to the neonate immediately after delivery
- Vitamin K administration does not achieve immediate reversal of maternal anticoagulation (which may persist for 24 hours); more rapid reversal requires the transfusion of fresh frozen plasma.
- Fetal levels of coagulation factors do not correlate with maternal levels, and infusion of fresh frozen plasma into the mother does not reliably reverse fetal anticoagulation.
- A cesarean delivery may prevent hemorrhagic fetal death, and fresh frozen plasma should be administered to the neonate.

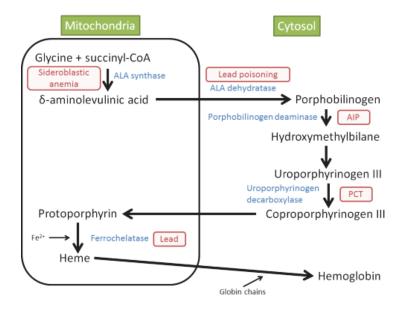
Porphyrias

AIP - porphobilinogen deAminase; PCT - uroporphyrinogen deCarboxylase

Overview

Acute intermittent porphyria: 6 P's

- · Porphobilinogen deaminase deficiency
- · Pain in abdomen (most common, 95% of patients experience)
- · Psychological symptoms (Anxiety, agitation, hallucination, hysteria, delirium, depression)
- · Peripheral neuropathy (Patchy numbness and paresthesias)
- · Pee abnormality (Dysuria, urinary retention/incontinence or dark urine)
- · Precipitated by drugs (e.g. barbiturates, oral contraceptives, Sulfa drugs)



Acute intermittent porphyria (AIP)

AIP can present with features of an acute abdomen, hypertension, psychiatric disturbance and hyponatraemia,

Aetiology

- autosomal dominant
- caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem.

Epidemiology

- The most common acute porphyria is acute intermittent porphyria.
- 20-40-year olds more likely to be affected (only rarely presents before puberty)
- AIP is more common in females (5:1)

Features

- 90% of affected individuals remain asymptomatic throughout their lives.
- · typically present with abdominal symptoms,
- neuropsychiatric symptoms
 - > Seizures occur in 10-20% of patients with acute intermittent porphyria (AIP).
 - A range of psychiatric symptoms, including hypomania and delirium may be seen.
- · hypertension and tachycardia
- · urine turns deep red on standing
- · Photosensitivity is unusual in AIP

Investigations

- Patients excrete urinary porphobilinogen (PBG) between and during acute attacks.
- Faecal porphyrin excretion is usually normal or slightly increased.
- All attacks of porphyria increase the activity of hepatic 5-aminolevulinate (ALA) synthase.
- Lab features
 - hyponatraemia,
 - > mild leukocytosis.

Diagnosis

- Urinary porphobilinogen assay is the optimal way to establish the diagnosis.
 - The best initial test
- diagnosis is <u>confirmed by</u> measuring erythrocyte <u>porphobilinogen</u> <u>deaminase</u> activity.

Factors precipitate an acute attack:

- Stress,
- Infection
- Pregnancy
- Menstruation
- starvation
- Drugs
 - sulphonamides,
 - barbiturates
 - > phenytoin.
 - Most anti-epileptics should not be given, but <u>qabapentin</u> is safe and the most appropriate choice for seizures occur in (AIP).
 - > ACE inhibitors and calcium channel blockers
 - Ibuprofen is safe for use in acute intermittent porphyria, but diclofenac should be avoided.

Acute intermittent porphyria: drugs

Drugs which may precipitate attack		Safe Drugs
 Alcohol Barbiturates Benzodiazepines Tricyclic antidepressants Halothane Oral contraceptive pill Sulphonamides Cephalosporins Erythromycin Isoniazid flucloxacillin Anabolic steroids 	Sulphonylureas Theophylline Antihistamines MAOIs Amiodarone Simvastatin. Diuretics calcium channel blockers ACE inhibitors	 Paracetamol Aspirin Ibuprofen Codeine Morphine Chlorpromazine β-blockers Gabapentin Penicillin Metformin amoxicillin

Treatment of seizures in AIP → Gabapentin

Treatment:

- decrease the activity of delta-aminolevulinic acid synthase (ALA)
 - glucose (carbohydrate loading)
 - high-glucose diets or infusions have been used for mild attacks of pain without neurological symptoms
 - intravenous haem arginate
 - thereby decreasing heme precursor synthesis.
 - The treatment of choice
- opiate analgesia.

Distinguishing between lead poisoning and acute intermittent porphyria

- Which one of the following features in an adult patient presenting with porphyrinuria would most suggest lead poisoning rather than acute intermittent porphyria as a cause?
 - Anaemia
 - Anaemia occurs only in lead poisoning and is due to:
 - inhibition of ferrochelatase (the activity of this enzyme is normal in acute intermittent porphyria)
 - a decrease in red cell lifespan
 - enzyme inhibition (pyrimidine 5'-nucleotidase) leading to the accumulation of pyrimidine nucleotides in red cells, which in turn reduces the stability of the cell membrane (and is seen on a blood film as basophilic stippling)

Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- mechanism
 - defect in uro-porphyrinogen decarboxylase

Aetiology

- inherited
 - most cases are sporadic
 - > may be inherited (autosomal dominant),
- acquired
 - > may be caused by hepatocyte damage e.g.
 - alcohol, (the commonest cause),
 - oestrogens (oral contraceptive pill)
 - excess iron (haemochromatosis)
 - hepatitis C

Features

- The most common presenting sign of PCT is <u>fragility of sun exposed skin after</u> <u>mechanical trauma</u>, leading to erosions and bullae, worst on dorsal hands, forearms, and face.
- · classically photosensitive rash with bullae,
 - > Bullae develop on sun-exposed areas
 - > When exposed to light, uroporphyrinogen generates free radicals that cause blistering of the skin.
 - > lesions heal slowly, leaving scars.
- skin fragility on face and dorsal aspect of hands

Investigations

- plasma total porphyrins
 - > The best initial test
 - > Porphyrins are increased in liver, plasma, urine and stool.
- Urine: elevated uroporphyrinogen (Urinary porphyrins) and pink fluorescence of urine under Wood's lamp
- Porphobilinogen (PBG) is normal.
- Assay of red blood cells for uroporphyrinogen decarboxylase (UROD) activity is now available
- Antinuclear antibodies are frequently seen

Management

- · withdrawal of the precipitant
- phlebotomy to deplete the excess iron stores that exacerbate the porphyria.
 - Venesection is effective (450 ml/week) until haemoglobin is 120 g/L.
- Chloroquine may also be effective because it promotes porphyrin excretion.

Variegate porphyria

- · autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- · abdominal and neurological symptoms
- more common in South Africans

Hodgkin's lymphoma (HL)

present at a younger age. Chest discomfort, including cough and shortness of breath, is common.

Hodgkin's lymphoma - most common type = nodular sclerosing

Hodgkin's lymphoma - best prognosis = lymphocyte predominant

Overview

- Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell.
- haematological malignancy arising from mature B cells.
- Lymphadenopathy, typically painless and most commonly involving the cervical and/or supraclavicular nodal chain, is the most common presenting symptom of HL.

Epidemiology

It has a bimodal age distributions being most common in the third and seventh decades

Risk factors

- · history of EBV infection
- · family history of Hodgkin's lymphoma
- · young adults from higher socio-economic class
- Immunodeficiency: e.g., organ or cell transplantation, immunosuppressants, HIV infection, chemotherapy
- Autoimmune diseases (e.g., rheumatoid arthritis, sarcoidosis)

Features

- Painless lymphadenopathy
 - ➤ Most common is cervical lymph nodes (in ~ 60–70% of patients)
- Mediastinal mass → chest pain, dry cough, and shortness of breath
- Splenomegaly or hepatomegaly may occur if the spleen or liver are involved.
- B symptoms
 - Night sweats.
 - > weight loss > 10% in the past 6 months,
 - fever > 38°C (100.4°F)
- Can occur in a variety of diseases, such as non-Hodgkin lymphoma, other malignancies, tuberculosis, and various inflammatory diseases
- Pel-Ebstein fever
 - ➤ Intermittent fever with periods of high temperature for 1–2 weeks, followed by afebrile periods for 1–2 weeks. Relatively rare but very specific for HL.
- Alcohol-induced pain
- Pruritus (focal or generalized)

Histological classification

Туре	Frequency	Prognosis	Notes
Nodular sclerosing	Most common (around 70%)	Good prognosis	More common in women. Associated with lacunar cells
Mixed cellularity	Around 20%	Good prognosis	Associated with a large number of Reed- Sternberg cells
Lymphocyte predominant	Around 5%	Best prognosis	
Lymphocyte depleted	Rare	Worst prognosis	

Poor prognosis

- weight loss > 10% in last 6 months
- fever > 38 C
- night sweats
- Other factors associated with a poor prognosis identified in a 1998 NEJM paper included:
 - > age > 45 years
 - stage IV disease
 - ➤ haemoglobin < 10.5 g/dl</p>
 - ➤ lymphocyte count < 600/l or < 8%
 - > male
 - > albumin < 40 g/l
 - > white blood count > 15,000/l
 - ➤ A mass of >10 cm in size

Fatigue, pruritus, EBV infection although they are common, BUT they have no prognostic significance.

Staging

Ann-Arbor staging of Hodgkin's lymphoma

- I: single lymph node
- II: 2 or more lymph nodes/regions on same side of diaphragm
- III: nodes on both sides of diaphragm
 - Spleen is regarded as a Lymph Node region, So lymphoma with splenomegaly -> Stage III
- IV: spread beyond lymph nodes

Each stage may be subdivided into A or B

- A = no systemic symptoms other than pruritus
- B = weight loss > 10% in last 6 months, fever > 38c, night sweats (poor prognosis)

Diagnosis

- Lymph node biopsy would be more likely to be positive, RSC is evident on microscopy.
- Bone marrow
 - Hodgkin results in <u>patchy</u> bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results.
 - ➤ Bone marrow biopsy is more useful for staging of advanced disease

Management:

• Early stage (IA or IIA): Radiotherapy and chemotherapy.

- Secondary malignancy is the long-term complication of the radiotherapy (need long term monitoring)
- Later stage (III, IVA or IVB): Chemotherapy alone.
- Large mass in chest regardless of stage: Radiotherapy and chemotherapy.
- Chemotherapy includes ABVD: Adriamycin (also known as Doxorubicin), Bleomycin,
 Vincristine. Doxorubicin. cyclophosphamide, prednisolone. Rituximab & others
 - > Bleomycin related pulmonary fibrosis is a major toxicity of the ABVD regimen
 - A high-resolution CT scan and pulmonary function tests are required to diagnose this condition.
 - Oxygen therapy should be used with caution in these patients as there is concern about further lung damage secondary to oxygen free radicals.
 - Although doxorubicin (also known as adriamycin) can cause cardiotoxicity, this is unusual at the doses used in this regimen and one would expect abnormalities on the ECG.
- Relapsed Hodgkin lymphoma → salvage chemotherapy followed by BEAM conditioned autologous stem cell transplantation as the established gold standard.

Prognosis is good overall, but it depends on classification and staging.

Hodgkin's lymphoma (HL)	Non-Hodgkin's lymphoma (NHL)
Younger age	Older age
more often restricted to lymph nodes in the neck.	Peripheral lymphadenopathy is common
Reed-Sternberg cells are present.	Reed-Sternberg cells are NOT present.
Extra-nodal involvement un common	Extra-nodal involvement is common

Non-Hodgkin's lymphoma (NHL) (NICE guideline 2016)

- include any kind of lymphoma except Hodgkin's lymphomas.
- Most of NHL are of B cell phenotype, although T cell tumours are increasingly being recognized.
- subtypes of non-Hodgkin's lymphoma (NHL):
 - > diffuse large B-cell lymphoma
 - Burkitt lymphoma.

Diagnosis

- Type of biopsy:
 - First line → excision biopsy
 - if not surgically feasible → needle core biopsy procedure
- in patient with histologically high-grade B-cell lymphoma:
 - ➤ use **FISH** (fluorescence in situ hybridisation) to identify a *MYC* rearrangement
 - ➤ If a MYC rearrangement is found, → use FISH to identify the immunoglobulin partner and the presence of BCL2 and BCL6 rearrangements.
- Indications of using FDG-PET-CT imaging (fluorodeoxyglucose-positron emission tomography-CT)
 - Staging
 - > to assess response at completion of planned treatment for:
 - diffuse large B- cell lymphoma
 - Burkitt lymphoma.
 - to assess response to treatment before autologous stem cell transplantation for high-grade (NHL).

Management

• follicular lymphoma

- Asymptomatic patients with low grade lymphoma such as follicular lymphoma (grade 1 and 2) can be observed closely (Wait and watch approach)
 - The value of intensive chemotherapy is questionable in asymptomatic patients. No long-term survival benefit has been demonstrated with this approach.
- > stage IIA → local radiotherapy as first-line
- > stage IIA + asymptomatic + single radiotherapy volume is not suitable →'watch and wait' (observation without therapy)
- > stage IIA + symptomatic + single radiotherapy volume is not suitable → treat
 as advanced-stage (stages III and IV) symptomatic
- ➤ advanced-stage (stages III and IV) asymptomatic → rituximab
- ➤ advanced-stage (stages III and IV) symptomatic → rituximab + combination with:
 - cyclophosphamide, vincristine and prednisolone (CVP)
 - cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
 - mitoxantrone, chlorambucil and prednisolone (MCP)
 - cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon- α (CHVPi) or
 - chlorambucil
- Relapsed or refractory advanced-stage (stages III and IV):
 - induction of remission → Rituximab + combination with chemotherapy
 - maintenance therapy → Rituximab monotherapy
 - in second or subsequent remission → stem cell transplantation

MALT lymphoma

- ➤ H. pylori-positive gastric MALT lymphoma → Helicobacter pylori eradication therapy
- → H. pylori-negative gastric MALT lymphoma → Helicobacter pylori eradication therapy
- > gastric MALT lymphoma that responds clinically and endoscopically
 to H. pylori eradication therapy but who have residual disease shown by surveillance
 biopsies of the stomach, + no high-risk features. → 'watch and wait' (observation
 without therapy)
- ➤ residual MALT lymphoma after H. pylori eradication therapy + high risk of progression [H. pylori- negative at initial presentation or t(11:18) translocation], →
 - chemotherapy (for example, chlorambucil or CVP) + rituximab OR
 - gastric radiotherapy.
- Non-gastric MALT lymphoma
 - localised disease sites → radiotherapy
 - if radiotherapy is not suitable or disseminated disease → chemotherapy (for example, chlorambucil or CVP) + rituximab
 - localised + asymptomatic + radiotherapy is not suitable → 'watch and wait' (observation without therapy)

• Mantle cell lymphoma

- ➤ advanced-stage , symptomatic → chemotherapy + rituximab
- ➤ localised stage I or II → radiotherapy
- ➤ non-progressive + asymptomatic + radiotherapy is not suitable → 'watch and wait' (observation without therapy)
- ➤ chemosensitive mantle cell lymphoma → autologous stem cell transplantation
- ➤ previously untreated + stem cell transplantation is unsuitable → Bortezomib

Haematological malignancies: genetics

Below is a brief summary of the common translocations associated with haematological malignancies

t(9;22) - Philadelphia chromosome

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17)

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

t(1:14)

 This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates BCL10

t(8;14)

- seen in Burkitt's lymphoma
- · MYC oncogene is translocated to an immunoglobulin gene

t(11;14)

- Mantle cell lymphoma
- · deregulation of the cyclin D1 (BCL-1) gene

t(11; 18)

 This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates MALT1

t(14;18)

- This translocation is associated with follicular lymphoma
- results in a chimeric heavy-chain Ig (chromosome 14) and BCL2 (chromosome 18) gene.
- This disease presents with painless "waxing and waning" lymphadenopathy in additional to constitutional symptoms.

Haematological malignancies: infections

Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- HTLV-1: Adult T-cell leukaemia/lymphoma
- HIV-1: High-grade B-cell lymphoma

Bacteria

Helicobacter pylori: gastric lymphoma (MALT)

Protozoa

malaria: Burkitt's lymphoma

Burkitt's lymphoma

Burkitt's lymphoma - c-myc gene translocation

Burkitt's lymphoma is a common cause of tumour lysis syndrome

- Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes, which results (in approximately 90% of the cases) from chromosome translocations that involve the Myc gene.
 - chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes.
- It is a high-grade B-cell neoplasm.
- There are two major forms:
 - 1. endemic (African) form: typically involves maxilla or mandible
 - 2. **sporadic** form:
 - abdominal (e.g. ileo-caecal) tumours are the most common form.
 - More common in patients with HIV
- Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14).
 - The classic chromosome translocation in Burkitt's lymphoma involves chromosome 8, the site of the MYC gene.
- The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form
 of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings

 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Management

- Management is with chemotherapy.
 - > This tends to produce a rapid response which may cause 'tumour lysis syndrome'.
 - Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce the risk of this occurring.
 - * *allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective
 - Complications of tumour lysis syndrome include:
 - Hyperkalaemia
 - Hyperphosphataemia
 - Hypocalcaemia
 - Hvperuricaemia
 - acute renal failure

Prognosis

- Localised Burkitt's is associated with around a 90% survival rate,
- although the prognosis is less good in adults.

Cancer in the UK

The most common causes of cancer in the UK are as follows*

 1. Breast 	 6. Non-Hodgkin's lymphoma
2. Lung3. Colorectal	7. Melanoma8. Stomach
 4. Prostate 	 9. Oesophagus
5. Bladder	10. Pancreas

The most common causes of death from cancer in the UK are as follows:

• 1. Lung	6. Oesophagus
 2. Colorectal 	 7. Stomach
 3. Breast 	8. Bladder
 4. Prostate 	 9. Non-Hodgkin's lymphoma
 5. Pancreas 	10. Ovarian

- Cancer is the cause of 26% of deaths in the UK, and is a more common cause of death than cardiovascular disease.
- Lung cancer is the biggest cancer killer in the UK (in both male and female), although breast cancer has the highest incidence

Acute lymphoblastic leukaemia (ALL)

Epidemiology

- ALL is a disease of children.
- Most common malignant disease in children
- Peak incidence: 2-5 years

Classification (The WHO classification)

- B-cell ALL (around 80-85% of cases)
- T-cell ALL (around 15–20% of cases)

Risk factors

- Children with certain genetic and immunodeficiency syndromes are at increased risk.
 These include:
 - Down syndrome,
 - Neurofibromatosis type 1,
 - Bloom syndrome, and
 - ataxia telangiectasia.

Features

- The most common presenting symptoms of ALL are nonspecific: <u>fever</u>, infection, bleeding, bone pain, or painless lymphadenopathy.
 - Fever and lymphadenopathy are rare in AML, but can be common first signs in ALL
- Testicular enlargement (rare finding)
- Airway obstruction (stridor, difficulty breathing) caused by mediastinal infiltration
- Meningeal leukemia (or leukemic meningitis) → headache, neck stiffness

Diagnosis

- Bone marrow aspirate or biopsy: confirmatory diagnostic tests
 - ➤ AML: > 20% myeloblasts in the bone marrow
 - > ALL: > 25% lymphoblasts in the bone marrow

^{*}excludes non-melanoma skin cancer

Prognostic features

Good prognostic factors	Poor prognostic factors
 French-American-British (FAB) L1 type common ALL pre-B phenotype low initial WBC del(9p) t(12;21) 	 FAB L3 type T or B cell surface markers Philadelphia translocation, t(9;22) t(8:14) the worst prognosis age < 2 years or > 10 years male sex CNS involvement high initial WBC (e.g. > 100 * 10⁹/l) non-Caucasian

 The 8:14 chromosomal translocation is associated with a particularly poor prognosis, and is found in approximately 1% of adults with ALL. The incidence of CNS involvement is very high at the point of diagnosis, and median event free survival after chemotherapy is only two months.

Treatment

- Before ALL treatment with chemotherapy, if blast cells count is very high (> 100 * 109/l) →
 the patient needs Leukapheresis to prevent sludge in of capillary beds, this can be lifesaving.
- Philadelphia positive ALL:
 - Chemotherapy + rituximab + Tyrosine Kinase Inhibitor
 - high dose chemotherapy (usually UKALL 14 or hyper-CVAD), together with the anti-CD20 monoclonal antibody rituximab and a tyrosine kinase inhibitor in view of the BCR-ABL positivity.
- Central nervous system (CNS) therapy (intrathecal) is indicated in all patients with ALL
- Lumber puncture (LP) should be delayed until chemotherapy has begun
- Allogeneic stem cell transplantation

Chronic lymphocytic leukaemia (CLL)

CLL - treatment: Fludarabine, Cyclophosphamide and Rituximab (FCR)

CLL - immunophenotyping is investigation of choice

CLL + anaemia with positive Coombs test → autoimmune haemolytic anaemia (AHA) → Prednisolone is the initial intervention of choice. rituximab is the second-line step.

Overview

 (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%)

Prevalence

- CLL is the most common form of leukemia found in adults in Western countries.
- generally, affects older populations (The median age at diagnosis is 72 years)

Features

· often none

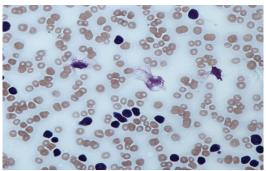
- · constitutional: anorexia, weight loss
- · bleeding, infections
- lymphadenopathy more marked than CML

Complications

- hypogammaglobulinaemia leading to recurrent infections
 - Infections are the most frequent complication causing death in patients with CLL.
 - Although intravenous immunoglobulin prevents recurrent infections it does not prolong survival.
- Autoimmune complications are common with CLL:
 - warm autoimmune haemolytic anaemia in 10-15% of patients
 - the combination of spherocytes with a raised bilirubin, LDH and positive direct Coombs' test is consistent with an autoimmune haemolysis.
 - immune thrombocytopenia (ITP)
 - ❖ the next step in management → Chemotherapy and intravenous immunoglobulin
 - ⇒ In ITP, platelets would only be indicated for life threatening bleeding (or platelet count <10 ×10⁹/L)
- transformation to high-grade lymphoma (Richter's transformation)

Investigations

- Blood film:
 - > smudge cells (also known as smear cells)
 - smudge cells are the artifacts produced by the lymphocytes damaged during the slide preparation.
 - ≥ 5000 monoclonal B lymphocytes/µl. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry.
- Immuno-phenotyping:
 - Peripheral blood <u>flow cytometry</u> is the most valuable test to confirm a diagnosis of CLL.
 - > will demonstrate the cells to be B-cells
 - CD5, CD19 and CD23 are characteristically positive.
- Although a bone marrow biopsy is not required for diagnosis, it is recommended for the
 diagnostic evaluation of unclear cytopaenias, or FISH or molecular genetics if peripheral
 blood cell lymphocytosis does not allow adequate immunophenotyping
- An extended FISH analysis is recommended before the start of therapy because the
 detection of additional cytogenetic abnormalities [del(11q) or trisomy 12] may have
 therapeutic consequences



Peripheral blood film showing smudge B cells

Management

- · observation policy is usual during the early stages of the disease.
- Indications for treatment
 - progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
 - Bone marrow compromise (stage C disease).
 - Lymphocyte doubling time of less than 12 months
 - massive (>10 cm) or progressive lymphadenopathy
 - > massive (>6 cm) or progressive splenomegaly
 - progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months</p>
 - > Immune complications, for example, ITP, autoimmune haemolysis
 - systemic symptoms: (Disabling B symptoms)
 - weight loss > 10% in previous 6 months,
 - fever >38 C for > 2 weeks,
 - extreme fatique,
 - night sweats

Drugs

- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients
- > monitoring by regular blood counts
- What antimicrobial prophylaxis should he receive before starting chemotherapy with fludarabine?
- → Co-trimoxazole
 - Fludarabine is a purine analogue that is phosphorylated intracellularly.
 - All of the purine analogues cause myelosuppression, but there is a significantly higher risk of patients developing Pneumocystis jirovecii pneumonia while on treatment.
 - Use of prophylactic co-trimoxazole (Septrin) has dramatically reduced the frequency of this severe opportunistic infection in these patients.
 - Co-trimoxazole should be continued after chemotherapy until the CD4 counts exceeds 200 cells/mm3 (0.2 ×109/L).
- Regular infusions of immunoglobulin to prevent infections
 - Recurrent infections are recognised in CLL due to hypogammaglobulinaemia and immune paresis; but are not an indication for disease control.

CLL prognostic factors

Poor prognostic factors (median survival 3-5 years)

- male sex
- age > 70 years
- lymphocyte count > 50
- prolymphocytes comprising more than 10% of blood lymphocytes
- lymphocyte doubling time < 12 months
- raised LDH
- CD38 expression positive
- deletions of part of the short arm of chromosome 17 (del 17p)

Chromosomal changes

- deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality, being seen in around 50% of patients. It is associated with a good prognosis
- deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a poor prognosis

Differential diagnosis

- mantle cell lymphoma (MCL)
 - These tumour cells express B-cell surface antigens and also expresses CD5, but usually not CD23.
 - For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence in situ hybridisation (FISH) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL.
- small lymphocytic lymphoma (SLL)
 - In the WHO classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity.
 - <u>CLL</u> is effectively the same disease as SLL except the disease is found mostly in the bone marrow or blood.
 - SLL is found mostly in lymph nodes
 - The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 5 × 10⁹/l.
 - SLL cells show the same immunophenotype as CLL.
 - ➤ The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible.
- monoclonal B-lymphocytosis' (MBL)
 - In absence of lymphadenopathy, organomegaly, cytopaenia and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/µl defines 'monoclonal B-lymphocytosis' (MBL)
 - > can be detected in 5% of subjects with normal blood count.
 - ➤ Progression to CLL occurs in 1%–2% of MBL cases per year.

Acute myeloid leukaemia (AML)

Acute myeloid leukaemia - poor prognosis: deletion of chromosome 5 or 7

Acute myeloid leukaemia - good prognosis: t(15;17)

- AML is the most common form of acute leukaemia in adults.
- It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.
- Acute leukemia is defined as an accumulation of more than 20 percent of immature blasts at the bone marrow.
 - Chronic myeloid leukaemia often ends in acute blastic transformation after a mean duration of approximately four years.
- classically associated with Down syndrome.
- Alkylating agents is a chemotherapy drug class that increases the risk of developing AML.
- characterized by cells with positive cytoplasmic staining for myeloperoxidase.
- The median age of onset of AML is <u>65 years</u>.

Presentation

- Vague and non-specific (flu-like symptoms)
- Due to pancytopenia (Infection, anaemia, bleeding)
- Splenomegaly may occur but typically mild and asymptomatic.
- LN swelling is rare.

- High total leucocyte count (TLC) leads to leucostasis and hyperviscosity → drowsiness and retinal vein dilatation.
- Blood film reveals white cells predominantly myeloblasts and promyelocytes.

Poor prognostic features

AML → Cytogenetics Karyotype is of most prognostic value.

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7
 - bone marrow cytogenetics are the <u>most important</u> aspect in determining prognosis in AMI

Good prognostic features

- Karyotype of bone marrow
 - patients with t(8:21) or chromosomes 16 inversion have a low risk of relapse

Classification - French-American-British (FAB)

- MO undifferentiated
- M1 without maturation
- M2 with granulocytic maturation
 - > the most common (25% of adult AML)
 - > associated with a t(8;21) translocation.
- M3 acute promyelocytic (APL)
 - has the best prognosis of all the subtypes of AML.
 - ➤ Unlike the other AML subtypes, APL is treated with all-trans retinoic acid (ATRA).
 - \rightarrow t(15:17)
- M4 granulocytic and monocytic maturation
 - associated with a t(16:16) translocation
- M5 monocytic
- M6 erythroleukaemia
- M7 megakaryoblastic

AML (monocytic) **M5**: high count of circulating blasts → may lead to symptoms of cellular hyperviscosity (headache, confusion, fits, coma) and tissue deposits of leukaemia cells (gums hypertrophy) with cells stain positive with Sudan Black and myeloperoxidase plus NES.

ALL cells characteristically stain positive for **PAS** (Periodic acid-Schiff) and **NSE** (Non-specific Esterase).

AML cells characteristically stain positive for **Sudan Black** and **myeloperoxidase**, but **M4** and **M5** cells stain positive for **NSE**, while **M6** cells stain positive for **PAS**.

Differentiating between A	LL and AML	
	ALL	AML
Presence of auer rods in blood	None	Always present
Presence of lymphoblasts in blood	Always present	May or may not be present
Bone and joint pain	More common	Less common

More common

More common

Management

- Combination chemotherapy including arabinosylcystosine after apheresis.
- Cytarabine and Anthracycline is considered the initial treatment of choice for patients with AML.

Bone marrow transplantation

Hepatosplenomegaly

Organ infiltration

- The aim would be to choose a fully matched sibling who was also CMV-negative.
- In general, fully HLA matched, CMV matched, male donors are preferred over fully HLA matched, CMV matched female donors. This is because of the <u>increased risk of graft versus host disease in stem cell donations from female donors to male recipients</u>.

Acute promyelocytic leukaemia (APML)

Acute promyelocytic leukaemia - t(15;17)

- APML, the M3 subtype of AML.
- The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management
- APML is associated with the t(15:17) translocation
 - > causes fusion of the PML and RAR-alpha genes.
 - In 95% of cases, retinoic acid receptor-alpha (RARA) gene on chromosome 17 is involved in a reciprocal translocation with the promyelocytic leukaemia gene (PML) on chromosome 15.
 - The mechanism underlying leukaemogenesis is aberrant fusion of 2 genes PML and RARA.

Features

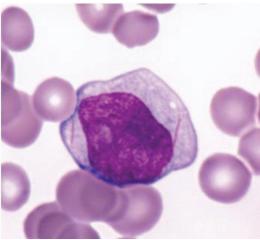
- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- Auer rods (seen with myeloperoxidase stain)
 - > Auer rods are eosinophilic needle-like cytoplasmic inclusions found in blast cells
- · good prognosis

management

- treatment of APML differs from that of all other AML forms
- the most appropriate initial treatment regimen: All trans retinoic acid (ATRA) a derivative of vitamin A., plus Anthracycline based chemotherapy

Less common

Ouite unusual



The distinct elongated cytoplasmic structures are Auer rods which are pathognomonic for AML.

Retinoic acid syndrome (or differentiation syndrome)

Pathophysiology

- thought to be the result of the release of cytokines and subsequent lung infiltration by the neutrophils created by the maturation of myelocytes in APML.
- The presence of CD13 expression on leukemic cells can be a predictor of the future development of this syndrome.

Causes

- after treatment of APML with all-trans retinoic acid (ATRA) (present within a week of treatment)
- after treatment of APML with arsenic trioxide.
- usually occurs during induction therapy

Incidence

• 14-16% of patients.

Features

- dyspnea, pulmonary edema and effusions, A chest X-ray shows interstitial infiltrates.
- fevers.
- · hypotension,
- Other complications include pericardial effusion, renal insufficiency, and hypertension.

treatment

- Corticosteroids
- the drug is temporarily stopped, then started again at 50-75% of the earlier dose. Alternatively, arsenic therapy can be tried.

prognosis

- Without prompt treatment with glucocorticoids, patients with this disorder have a mortality rate as high as 30% due to brain edema or hypoxemic respiratory failure.
- Fortunately, most patients improve markedly within 12 hours and their symptoms resolved completely within 24 hours.

Chronic myeloid leukaemia (CML)

Chronic myeloid leukaemia – imatinib = tyrosine kinase inhibitor

CML- Philadelphia chromosome – t(9:22)

Philadelphia translocation, t(9:22) - good prognosis in CML, poor prognosis in AML + ALL

Pathophysiology

- The Philadelphia chromosome is present in more than 95% of patients with (CML).
- It is due to a translocation between the long arm of chromosome 9 and 22 t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Epidemiology

- Sex: ♂ > ♀
- Peak incidence: 50-60 years

Etiology

- Idiopathic (in most cases)
- Ionizing radiation (e.g., secondary to therapeutic radiation)
- Aromatic hydrocarbons (especially benzene)

Features

- middle-age (40-50 years)
- anaemia.
- · weight loss,
- splenomegaly may be marked → abdominal discomfort

Complications

may undergo blast transformation (AML in 80%, ALL in 20%)

Investigations

- Peripheral blood
 - > spectrum of myeloid cells seen
 - The blood film shows both mature (neutrophils) and immature forms in various stages of differentiation (myelocytes and metamyelocytes)
 - In acute myelogenous leukemia (AML) one would expect only immature blasts.
 - CML causes the most severe leukocytosis (> 500,000/µl) of all forms of leukemia
 - Increasing basophilia is a sign of acceleration!
- Cytogenetic analysis of the patient's bone marrow
 - the most useful test
 - most cases of CML are usually associated with <u>BCR-ABL translocation</u>, (Philadelphia chromosome)
 - > Better than molecular analysis of peripheral blood
- Molecular analysis of peripheral blood
 - useful and least invasive for the patient

- BCR-ABL translocation (t[9:22]) can be detected by PCR
- however, in practice one would still eventually proceed to a bone marrow (BM) examination to assess morphology and you would still also perform conventional cytogenetics on the bone marrow (this is done on a bone marrow sample rather than peripheral blood because the cellularity tends to be greater in the BM, giving lower failure rates of the test).
- Leukocyte alkaline phosphatase (LAP) → decreased
 - Low LAP is a distinct feature of CML that distinguishes it from all other forms of leukemia

WHO classification of the CML phases

CML Phase	Blast count in peripheral blood and bone marrow
Chronic	< 10%
Accelerated	10–19%
Blast	≥ 20%

Management

- Unlike (CLL), CML will progress to frank leukaemia quite rapidly, so treatment is needed.
- imatinib is now considered first-line treatment
 - > inhibitor of the tyrosine kinase associated with the BCR-ABL defect
 - very high response rate in chronic phase CML
- If remission is not achieved with **imatinib**, then:
 - in a patient under 60-65 years, an allogeneic transplant would be considered if there was a matched sibling donor;
 - in a 50-year-old patient or younger a matched unrelated donor transplant would be considered too.
- If the patient had been in blast crisis phase, then AML-type chemotherapy as well as Glivec (imatinib) would be the choice.
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Allogenic bone marrow transplant

Complication

Cytomegalovirus pneumonia

- The microscopy shows owl's eye inclusion bodies, characteristic of CMV, but diagnosis is usually made by PCR of blood/lavage fluid.
- It is the commonest life-threatening complication following allogenic bone marrow transplant,
- usually occurring within the first 4 months following surgery.
- the treatment of choice → Ganciclovir
- Onset is rapid and mortality in the context of BMT is around 80%, even with antiviral therapy (ganciclovir).

Hairy cell leukaemia

Overview

- malignant proliferation disorder of B cells.
- · Rare, about 2% of leukemias.
- more common in males (4:1)
- frequently occurs in men in their fifth decade.

Features

- pancytopenia
- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphotase (TRAP) stain positive
- characteristic hairy leukocyte on blood smear with a "fried egg" appearance
 - > medium-sized lymphocytes with numerous spiky, peripheral, cytoplasmic projections.

Management

- chemotherapy is first-line: cladribine (adenosine deaminase inhibitor), pentostatin
 - > Cladribine
 - Cladribine is a purine analog → inhibit DNA polymerase and cause DNA strand breaks.
 - SE → myelosuppression, nephrotoxicity, and neurotoxicity.
- immunotherapy is second-line: rituximab, interferon-alpha
 - Alpha interferon at 2 million U/m2 subcutaneously three times a week for 12-18 months can be used to salvage relapsed or refractory hairy cell leukemia.

Paraproteinaemia

Causes of paraproteinaemia

- myeloma
- monoclonal gammopathy of uncertain significance (MGUS)
- benign monoclonal gammopathy
- · Waldenstrom's macroglobulinaemia
- amvloidosis
- · CLL, lymphoma
- · heavy chain disease
- POEMS

Benign monoclonal gammopathy

- non-lymphoid malignancy (e.g. colon, breast)
- · infections (CMV, hepatitis)
- autoimmune disorders (RA, SLE)

Multiple myeloma

classic symptoms of multiple myeloma: bone pain, pathological fracture, anaemia and hypercalcaemia (leading to thirst).

Multiple myeloma causes a low anion gap.

Definition

• Multiple myeloma is a neoplasm of the bone marrow plasma cells.

Epidemiology

• The peak incidence is patients aged 60-70 years.

- Multiple myeloma is the most common primary tumor of the bone in patients older than 50 years.
- · equal sex ratio
- more common in Afro-Caribbean ethnic groups than in Caucasians

Monoclonal products produced

- IgG (50-60%)
- IgA (20-30%)
- light chain disease (20%)

Association

• Type 2/Proximal renal tubular acidosis is a type of renal tubular acidosis associated with multiple myeloma.

Pathophysiology

- Neoplastic proliferation of plasma cells
 - ➢ Bone marrow infiltration → suppression of hematopoiesis → leukopenia, thrombocytopenia, anemia
 - ➤ Cell proliferation → osteolysis → hypercalcemia
- Overproduction of monoclonal immunoglobulin and/or light chains
 - Non-functioning antibodies → functional antibody deficiency
 - ➤ ↑ Serum viscosity → hyperviscosity syndrome

Clinical features

- · bone disease:
 - due to neoplastic plasma cells activating RANKL receptors on osteoclasts.
 - **bone pain**, (Bones commonly affected are the flat bones of the spine, and as such lower back pain is one of the most common presenting features)
 - > osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
 - weakness and paresthesias in the lower extremities due to vertebral compression fractures
- anaemia
 - fatique and malaise
 - > The most common presenting manifestations of multiple myeloma are those related to anemia.
- infection
- hypercalcaemia → nausea, fatique, confusion, polyuria, constipation
- hyperphosphataemia
 - due to reduced renal excretion which may be directly due to renal impairment or interference with excessive protein load.
- · Foamy urine,
 - > caused by Bence Jones proteinuria
- · renal failure
 - > the most common cause is from **light chain deposition**.
 - Usually, the renal damage in MM is tubular. Occasionally there may be glomerular damage with consequent albumin loss.
- amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity
 - carpal tunnel syndrome the most common peripheral neuropathy associated with multiple myeloma
- Multiple myeloma may present with roleaux formation on blood film and raised total protein (globulin component).
 - > The globulin level is markedly raised (albumin + globulin = total protein), suggesting the presence of a paraprotein.
 - (globulin level = total protein albumin). A normal level should be below 36 g/L.
- Hypercalcaemia in myeloma
 - primary factor:

- due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- > much less common contributing factors:
 - impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels

Which acid-base disorders may be found in an IgG multiple myeloma?

- **▶** Low anion-gap metabolic acidosis
 - IgG tends to be cationic, whereas IgA tends to be anionic. As a consequence, patients with IgG myeloma will tend to have a lower than normal serum anion gap.

Diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

- Major criteria
 - > Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
 - > 30% plasma cells in a bone marrow sample
 - > Elevated levels of M protein in the blood or urine
 - monoclonal proteins:
 - ❖ in the serum → (usually IgG or IgA)
 - in the urine (Bence Jones proteins)
 - there is Negative dipstick for protein and positive in biochemistry, because Bence jones proteins are not detected by dipstick
- Minor criteria
 - > 10% to 30% plasma cells in a bone marrow sample.
 - Minor elevations in the level of M protein in the blood or urine.
 - > Osteolytic lesions (as demonstrated on imaging studies).
 - > Low levels of antibodies (not produced by the cancer cells) in the blood.

Investigations: (NICE 2016)

- 1. to confirm the presence of a paraprotein indicating possible myeloma or (MGUS):
 - > serum protein electrophoresis and serum-free light-chain assay
 - (best initial test) → serum protein electrophoresis
 - ➤ If serum protein electrophoresis is abnormal → use serum immunofixation
 - Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma.
 - The observation that serum free light chains can occur in the absence of a detectable monoclonal protein in the peripheral blood is the explanation why two tests must always be done when investigating possible myeloma: both serum electrophoresis and either serum or urinary free light chains.
 - monoclonal free light chains are found in isolation in 20–30% of cases of myeloma
- 2. to confirm a diagnosis of myeloma:
 - bone marrow aspirate and trephine biopsy
 - > the bone marrow aspirate would confirm the diagnosis irrefutably.
 - morphology to determine plasma cell percentage
 - Bone marrow examination would reveal increased plasma cells (greater than 4% and usually greater than 30%).
 - flow cytometry to determine plasma cell phenotype
 - bone marrow aspirate → dark red jelly-like material in the syringe (Plasma cells)

- 3. in a patient presenting with spinal cord compression:
 - > the most appropriate <u>initial</u> investigation is → Urgent MRI of her spine
 - This should be done before investigation that used to confirm myeloma.
 - ➤ skeletal survey → bone lesions

Laboratory confirmation of Multiple Myeloma (NICE 2018)

- To confirm the presence of a paraprotein indicating possible myeloma or (MGUS):
 - Two tests must always be done: both serum electrophoresis and either serum or urinary free light chains
 - If serum protein electrophoresis is abnormal, use serum immunofixation to confirm the presence of a paraprotein indicating possible myeloma or MGUS.
 - Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence–Jones protein assessment) alone to exclude a diagnosis of myeloma.
 - free light chains (20–30% of cases of myeloma) are found in the absence of a detectable monoclonal protein in the peripheral blood.
- 2. To confirm a diagnosis of myeloma:
 - Bone marrow aspirate and trephine biopsy
 - Morphology to determine plasma cell percentage (≥10%).
 - flow cytometry to determine plasma cell phenotype.

Treatment: general view

- The best initial treatment of multiple myeloma is <u>chemotherapy</u> induction.
- autologous bone marrow transplant in addition to chemotherapy has better results than chemotherapy alone.
- Asymptomatic patients: → watch and wait, unless patients have:
 - ≥ 60% clonal cells,
 - > excessive free light chains or
 - ≥ 1 bone lesion
- Symptomatic patients
 - HCT eligible: induction therapy followed by autologous HCT
 - > HCT ineligible: chemotherapy alone (e.g., dexamethasone and lenalidomide)
- Supportive therapy
 - Osteolysis and bone pain
 - Bisphosphonates
 - Radiation therapy of osteolytic regions
 - > Pancytopenia with anemia and increased risk of infection
 - Blood transfusions
 - Granulocyte-colony stimulating factor (G-CSF) and erythropoietin (EPO)

Patients with myeloma with high paraprotein levels and symptoms related to hyperviscosity should have urgent plasma exchange, chemotherapy needs to then be instituted promptly to control the disease process and prevent symptoms reoccurring.

Treatment

- previously untreated multiple myeloma (newly diagnosed)
 - Patients who are eligible for high-dose chemotherapy with stem cell transplantation
 - bortezomib + dexamethasone,
 - **or** bortezomib + dexamethasone + thalidomide
 - if high-dose chemotherapy with stem cell transplantation is considered inappropriate
 - thalidomide + alkylating agent + corticosteroid
- People who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation:
 - bortezomib (a proteasome inhibitor) monotherapy
- People who have received two or more prior therapies:
 - ➢ lenalidomide + dexamethasone
 - lenalidomide → immunomodulatory derivatives (structural derivatives of thalidomide)
- People with untreated, newly diagnosed, myeloma-induced acute renal disease:
 - bortezomib + dexamethasone
 - ➤ If a bortezomib is unsuitable → thalidomide + dexamethasone
 - > Do not perform plasma exchange for myeloma-induced acute renal disease.
- · Preventing bone disease, managing non-spinal and spinal bone disease
 - bisphosphonates should be given <u>routinely</u>, even in the absence of hypercalcaemia.
 - Bisphosphonates reduce bony disease in myeloma, lowering the frequency of pathological fractures, modulate the disease and have some antitumor activity.
 - zoledronic acid or
 - disodium pamidronate, if zoledronic acid is contraindicated or not tolerated or
 - sodium clodronate, if zoledronic acid and disodium pamidronate are contraindicated, not tolerated or not suitable
 - surgical stabilisation followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures.
 - Consider radiotherapy for people who need additional pain relief
- Managing peripheral neuropathy
 - > If patient on bortezomib
 - switch to subcutaneous injections and/or
 - reduce to weekly doses and/or
 - reduce the dose.
 - > if patient on other than bortezomib
 - Temporarily stop neuropathy-inducing myeloma treatments if people develop either of the following:
 - grade 2 neuropathy with pain
 - grade 3 or 4 neuropathy
- Managing fatigue
 - Erythropoietin analogues (adjusted to maintain a steady state of haemoglobin at 110–120 g/litre) to improve fatigue in people with myeloma who have symptomatic anaemia.
- Cord compression secondary to bony involvement of multiple myeloma:
 - > I.V Steroids should be commenced immediately
 - Melphalan and dexamethasone both have a place in the treatment of myeloma but would not be of use as pain control.
 - However, the treatment of choice is local radiotherapy. NICE suggest localised radiotherapy should be the first point of call for urgent treatment.
 - Radiotherapy is extremely effective as <u>pain control</u> in this situation and would be the ideal choice.
 - Vertebroplasty is typically considered in patients of whom have evidence of metastatic changes in the spine but show no signs of spinal cord compression.

Surgical decompression: is also considered if imaging suggests any form of spinal instability or structural defects, but often after steroids and radiotherapy has been administered.

Blood transfusion in myeloma may cause acute deterioration

- The plasma volume increases with increasing viscosity and may compromise cardiac function.
- They should not be transfused until the viscosity has been lowered as a rise in haematocrit
 can precipitate a serious worsening of their symptoms.

Thalidomide

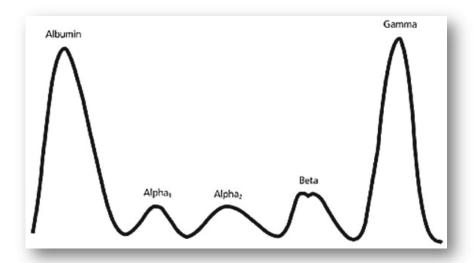
- Immunomodulatory drugs such as thalidomide and lenalidomide are now first line medications in the treatment of myeloma.
- The most common side effect of lenalidomide is myelosuppression, whereas somnolence, peripheral neuropathy and constipation are side effects of thalidomide.
- The inherent, serious issue that is applicable to both medications is the teratogenic
 potential all patients must be informed of this risk and advised regarding birth
 control and avoidance of sharing of medications with any other person.
- It is not known whether lenalidomide is present in the semen of male patients receiving the
 drug. Therefore, males receiving lenalidomide must always use a latex condom during any
 sexual contact with females of childbearing potential even if they have undergone a
 successful vasectomy.

Myeloma: prognosis

- B2-microglobulin is a useful marker of prognosis raised levels imply poor prognosis.
 - > Beta-2-microglobulin has been shown to be predictive of risk of progression of disease in myeloma, myelodysplastic syndrome, and chronic myeloid leukaemia.
 - In myeloma it is an accurate estimate of total disease load, with guidelines suggesting that a beta-2-microglobulin level of >3.5 mg/L is strongly associated with increased mortality and morbidity.
- Low levels of albumin are also associated with a poor prognosis
- Increased lactate dehydrogenase levels more than double the normal is considered a
 bad prognostic sign in multiple myeloma.

International prognostic index

Stage	Criteria	Median survival (months)
I	B2 microglobulin < 3.5 mg/l Albumin > 35 g/l	62
II	Not I or III	45
Ш	B2 microglobulin > 5.5 mg/l	29



Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region.

 In the interpretation of serum protein electrophoresis, most attention focuses on the gamma region(gamma-globulin zone), which is composed predominantly of antibodies of the IgG type.

Monoclonal gammopathy of undetermined significance (MGUS)

- MGUS also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below.
- can be seen in >5% of people over 70 years of age.

Risk of transmission to malignancy:

- Around 10% of patients eventually develop myeloma at 5 years, with 50% at 15 years
- 1 percent per year develop multiple myeloma.

Features

- usually asymptomatic
- no bone pain or increased risk of infections
- around 10-30% of patients have a demyelinating neuropathy

Differentiating features from myeloma

- normal immune function
- normal beta-2 microglobulin levels
- lower level of paraproteinaemia than myeloma (e.g. < 30g/l lgG, or < 20g/l lgA)
- stable level of paraproteinaemia
- no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

feature	MGUS	myeloma
M protein concentration in serum	<30 g/l	>30 g/l
bone marrow plasma cells	<10 %	>10 %
organ and tissue impairment	no end organ damage including bone lesions	organ or tissue impairment (including bone lesions)

Treatment

- Observation
- if there is neuropathy
 - MGUS patients are associated with osteoporosis and osteopenia. They may benefit from treatment with bisphosphonates
 - Bisphosphonates
 - pyrophosphate analogue
 - act by binding to hydroxyapatite in bone which leads to low osteoclastic activity.

MRCPUK-part-2-March- 2017: A 72-year-old man C/O persistent tiredness over the past 3 months. No other abnormality. Investigations reveals Albumin: 38 g/l, IgG paraprotein band: 14 g/l, Bone marrow: 7% plasma cells. Which of the following is the most appropriate intervention?

→ Observation

- MGUS is defined by paraprotein (<30 g/l), bone marrow plasma cells <10% and the absence of myeloma-related organ or tissue damage (predominantly renal, skeletal or bone marrow impairment).
- Annual overall progression to myeloma is 1% and, as such, no intervention is required.

Smoldering myeloma

- Smoldering multiple myeloma → multiple myeloma (M-protein >3g/dL or >10% plasma cells in bone marrow) + no end organ damage.
- criteria for end-organ damage, which are:
 - Serum calcium >11.5 mg/dL
 - > Serum creatinine >2 mg/dL or estimated creatinine clearance <40 ml/min
 - Anemia with hemoglobin <10 g/dL</p>
 - > Bone lesions: osteolytic, pathological fracture; osteopenia
- Treatment → Observe and monitor

Non-secretory myeloma

Bone marrow clonal plasma cells =10%, Myeloma-related end-organ damage, No M
protein in blood or urine

Thymoma are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

Associated with

- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also: SLE, SIADH

Causes of death

- · compression of airway
- cardiac tamponade

Tumour lysis syndrome (TLS)

Rasburicase - a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin

• Tumour lysis syndrome (TLS) is a potentially deadly condition

Causes:

- treatment of high grade lymphomas and leukaemias.
- It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy.

Pathophysiology:

• breakdown of the tumour cells and the subsequent release of chemicals from the cell.

Features:

- high potassium
- · high phosphate
- low calcium.
- It should be suspected in any patient presenting with an acute kidney injury in the
 presence of a high phosphate and high uric acid level.

Diagnosis:

- From 2004 TLS has been graded using the Cairo-Bishop scoring system <u>Laboratory tumor lysis syndrome</u>: abnormality in two or more of the following, occurring
 within three days before or seven days after chemotherapy.
 - > uric acid > 475umol/l or 25% increase
 - potassium > 6 mmol/l or 25% increase
 - phosphate > 1.125mmol/l or 25% increase
 - > calcium < 1.75mmol/l or 25% decrease
- <u>Clinical tumor lysis syndrome</u>: laboratory tumor lysis syndrome plus one or more of the following:
 - increased serum creatinine (1.5 times upper limit of normal)
 - > cardiac arrhythmia or sudden death
 - > seizure

Management of acute tumour lysis syndrome

- aggressive hydration, aiming for 3 L/m² control of electrolyte disturbances (typically, hypocalcaemia, hyperphosphataemia, hyperkalaemia and uraemia)
- clearance of the increased metabolic load with rasburicase, a specific recombinant enzyme.

Prevention:

- Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy.
 - Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water soluble than uric acid and is therefore more easily excreted by the kidneys.
 - The commonest reported side effect of rasburicase is fever.
 - rasburicase overdose may lead to accumulation of hydrogen peroxide.
- patients at low risk → oral allopurinol during chemotherapy
- Other options for the management of tumour lysis syndrome include
 - Acetazolamide to drive urine alkalinisation.

Waldenstrom's macroglobulinaemia

IgM paraproteinaemia - ?Waldenstrom's macroglobulinaemia

Overview

- It is a lymphoplasmacytoid malignancy seen in older men, characterised by the secretion of a monoclonal IgM paraprotein,
- indolent B-cell lymphoma
- Also known as Lymphoplasmacytoid lymphoma
- most common in older white men

Pathophysiology

- monoclonal IgM production by a malignant lymphoplasmacytic clone that can cause damage to multiple organs.
- The tumor cells in Waldenstrom macroglobulinemia are positive to CD20 markers.

Features

- · monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- hyperviscosity syndrome e.g.:
 - visual disturbance.
 - > neurological symptoms such as headache, dizziness, and vertigo
 - > raynaud phenomenon
- Bleeding is a possible complication as viscous serum causes defective platelet aggregation.
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

Investigations

- protein electrophoresis → elevated IgM
- Bone marrow biopsy (the gold standard for the diagnosis)
 - ➤ Shows → abnormal plasma cells with **Dutcher bodies** (intranuclear inclusions of IgM deposits)
- Plasma viscosity
 - plasma viscosity measurement is essential to diagnose and initiate treatment. The initial treatment would be plasmapheresis followed by cytoreductive therapy.

Differential diagnosis

- multiple myeloma
 - usually presents with IgG or IgA secretion and lytic bone lesions.
- Waldenström's
 - In an elderly patient found to have a large IgM-kappa paraprotein, which feature will help to decide whether it is related to Waldenström's macroglobulinaemia?
 - No isotype suppression
 - Isotype suppression (<u>normal IgG and IgA levels</u>) is more a feature of myeloma than Waldenström's macroglobulinaemia and is therefore a good differentiator.

Treatment

- Asymptomatic → Follow-up
 - treatment only indicated in symptomatic patients
- Causative: CD20 antibodies (e.g., rituximab)
- Hyperviscosity syndrome: plasmapheresis

ECOG score

- The ECOG score (Eastern Cooperative Oncology Group (ECOG) score) is a 'performance status' scale, or a score that measures the functional status of a patient.
- It is used to decide if a patient is a good or poor candidate for future oncological therapies.
- Those with a poor functional status is a poor candidate for further chemotherapy.

0	Fully active, able to carry on all pre-disease performance without restriction		
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work		
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours		
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours		
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair		
5	Dead		

Tumour markers

Tumour markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- · tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

Monoclonal antibodies

Tumour marker	Association
CA 125	Ovarian cancer primary peritoneal cancer
CA 19-9	Pancreatic cancer
CA 15-3	Breast cancer

Tumour antigens

Tumour marker	Association
Prostate specific antigen (PSA)	Prostatic carcinoma
Alpha-feto protein (AFP)	Hepatocellular carcinoma, teratoma, non-seminomatous germ-cell tumours
Carcinoembryonic antigen (CEA)	Colorectal cancer
S-100	Melanoma, schwannomas
Bombesin	Small cell lung carcinoma, gastric cancer, neuroblastoma
β-human chorionic gonadotrophin	choriocarcinomas, germ-cell tumours and lung cancers

- Bence Jones protein → specific for myeloma. false positives are rare, and therefore it is more specific than the other markers. The most specific tumour marker
- Alpha-fetoprotein (AFP), beta-hCG and PLAP (placental like isoenzyme of alkaline phosphatase) are the major tumour markers in use for the monitoring of testicular teratoma.

Common tumor markers		
Tumor marker Associated conditions		
Alpha fetoprotein (AFP)	 Hepatocellular carcinoma (HCC) Hepatoblastoma Yolk sac tumor of the ovary (endodermal sinus tumor) Mixed germ cell tumor 	
	 Transient elevation during pregnancy ↑ AFP: abdominal wall defects, neural tube defects ↓ AFP: associated with trisomy 21, 18, and 13 (See prenatal diagnostics for details) 	
β-HCG	 Testicular germ cell tumors (choriocarcinoma, embryonal cell carcinoma, mixed germ cell tumor, seminoma) Ovarian cancer: choriocarcinoma (gestational trophoblastic disease) 	
	If detectable in urine Pregnancy marker Molar pregnancy (hydatidiform mole)	
Carcinoembryonic antigen (CEA)	 Colorectal cancer Pancreatic cancer Breast cancer Lung cancer (especially in non-small cell cancers) 	

Common tumor markers			
Tumor marker	Associated conditions		
	Gastric cancer Endometrial cancer Medullary thyroid cancer		
	Smokers		
Prostate-specific antigen (PSA)	Prostate cancer		
anugen (FSA)	Benign prostatic hyperplasiaProstatitis		
Calcitonin	Medullary thyroid cancer		
Alkaline phosphatase	Metastases to bone or liver		
	Paget disease of the bone		
Lactate dehydrogenase (LDH)	 Ovarian cancer (dysgerminoma) Testicular germ cell tumors (both seminoma and nonseminoma) Lymphomas Ewing's sarcoma 		
	HepatitisHemolysisMyocardial infarction		
Neuron specific enolase (NSE)	Small cell lung cancerNeuroendocrine tumorsNeuroblastoma		
	NSE is released secondary to brain injury (e.g., stroke)		
CA 19-9	Pancreatic adenocarcinoma		
CA 15-3/CA 27-29	Breast cancer		
CA 125	Ovarian carcinoma(80–100%)		
Chromogranin A	Neuroendocrine tumorsMedullary thyroid cancer		
S-100 protein (S100A) and (S100B)	Malignant melanoma		
β2 microglobulin (β2M)	Multiple myelomaChronic lymphocytic leukemiaRenal disease		
Thyroglobulin	Papillary thyroid carcinomaFollicular thyroid carcinoma		
Monoclonal immunoglobulins	Multiple myelomaWaldenstroms macroglobulinemia		
	 Monoclonal gammopathy Infections Certain autoimmune conditions (e.g., rheumatoid arthritis) 		

Neutropenic sepsis (Febrile neutropenia)

Definition

- Neutropenic sepsis is a relatively common complication of cancer therapy (chemotherapy).
- It most commonly occurs 7-14 days after chemotherapy.
- It may be defined as a neutrophil count of < 0.5 * 10⁹ in a patient who is having anticancer treatment and has one of the following:
 - > a temperature higher than 38 C or
 - > other signs or symptoms consistent with clinically significant sepsis

Causes

Neutropenic patients should avoid cold meats, soft cheese and dairy products due to risk of listeriosis

- in the majority of them identifying a source of the temperature can be impossible.
- the most common pathogens are now gram-positive organisms. such as Staphylococcus epidermidis or Streptococcus viridans (around 60% of cases)
- Source of infection
 - In neutropenic patients, almost any site can be the source.
 - ➤ Indwelling lines → Staph.epidermidis infection
 - ➤ mucositis or previous quinolone treatment → viridans streptococci

Mucositis can be a source of neutropenic sepsis → Swab mouth ulcer

Risk factors

- Age > 65
- Albumin less than 35 g/l
- Hepatic disfunction
- Baseline neutrophil less than 1.5 * 10⁹
- Planned relative dose intensity > 80%

Prophylaxis

• if it is anticipated that patients are likely to have a neutrophil count of < 0.5 * 10⁹ as a consequence of their treatment they should be offered a fluoroguinolone

Management

- antibiotics must be started immediately, do not wait for the WBC, (N.B. after taking cultures).
- · First-step:
 - NICE recommend starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
 - piperacillin with tazobactam with gentamicin is the preferred first-line option according to Christies guidelines for patient who are not allergic to penicillin and have no significant renal impairment.
 - If there is penicillin allergy → meropenem 1g three times a day is an appropriate option
 - Dose adjustment may be needed where the GFR is less than 50 ml/min
 - many units add vancomycin if the patient has central venous access, but NICE do not support this approach
 - ➤ assessment the patient at 48 hours, If they have improved and the temperature has settled → Convert patient to oral antibiotics and discharge

 NICE does not recommend keeping patients in hospital whilst waiting for their neutrophil count to improve.

Second-step:

> if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin

Third-step:

- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting antifungal therapy blindly
- there may be a role for G-CSF (filgrastim) in selected patients
 - if the neutropenic sepsis has responded well to treatment, but is still neutropenic, could be given G-CSF to stimulate a neutrophilia to help restore his cell counts quicker and reduce the chance of developing another episode of neutropenic sepsis.
 - Side-effect of G-CSF (filgrastim):
 - Filgrastim stimulates a white cell count which can increase far above the normal range, and the white cell count will return to normal once it is stopped.

Neutropenic sepsis with no response to antibiotics at 48 hrs → possible fungal infection

Gram colony stimulating factor (G-CSF) can be used to boost neutrophil numbers in neutropenia

MRCPUK-part-1-May 2016 exam: When is the risk of febrile neutropenia thought to be highest following chemotherapy?

→ 10 days in to treatment

Assessment of neutropenia

Definition and classification

- absolute neutrophil count (ANC) <1500/microlitre or <1.5 x 10^9/L is defined as neutropenia and graded as mild, moderate, severe, or very severe:
 - Mild: 1000 to 1500/microlitre or 1 to 1.5 x 10^9/L
 - Moderate: 500 to 999/microlitre or 0.5 to 0.99 x 10^9/L
 - Severe: 200 to 499/microlitre or 0.2 to 0.49 x 10^9/L
 - Very severe: <200/microlitre or <0.2 x 10^9/L.</p>
- As the ANC falls below 1000/microlitre or 1 x 10⁴/L, the risk of infection progressively increases.
- If the ANC falls below 500/microlitre or **0.5 x 10^9/L**, infections may be **life-threatening**.
 - > However, there are some diseases, such as autoimmune neutropenia (AIN), in which a low ANC does not confer an infection risk; infections are rare in these patients despite the ANC often being <500/microlitre or <0.5 x 10^9/L.
- The ANC varies according to age and ethnicity.
 - > It is lower in children than in adults.
 - Black people and some Arab populations display lower average values.
 - The normal range in black people has a lower limit of 1400/microlitre or 1.4 x 10^9/L.

Causes

- Infections (the most common causes of neutropenia in adults),
- drug-induced neutropenias
- Acquired bone marrow diseases such as the leukaemias, lymphomas, and aplastic anaemia
- nutritional deficiencies (vitamin B12, folate, copper)

Systemic mastocytosis

Systemic mastocytosis results from a neoplastic proliferation of mast cells

Features

- urticaria pigmentosa produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- · monocytosis on the blood film

Diagnosis

- raised serum tryptase levels
- urinary histamine

Cervical cancer

- Cervical cancer is the most common cancer worldwide
- The incidence of cervical cancer peaks around the 6th decade.
- It may be divided into
 - squamous cell cancer (80%)
 - adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Risk factors

- human papilloma virus (HPV) 16,18 & 33 → the most common
 - associated with HPV 16 and 18 in approximately 70% of cases.
 - New vaccines are currently available in the United Kingdom to help immunise against this virus and hopefully prevent future cases of cervical cancer.
- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*
 - *the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov confirmed the link

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

Ovarian tumours

Ovarian cancer screening is not recommended in the general population as no survival benefit from earlier diagnosis and therapy has been shown.

- germ cell tumours
 - Patients are usually young.
 - most commonly seen in adolescents due to embryologic remnants
 - early pulmonary metastases
 - The fact that this lady is young, and has early pulmonary metastases, make a germ cell tumour much more likely
- The diagnosis is usually made on biopsy in the case of ovarian tumours.
- treatment usually consists of surgery followed by chemotherapy (BEP).
- Epithelial cell tumours
 - usually disseminate through the abdomen and peritoneum prior to metastasising to the lungs.
- Markers such as AFP, β -human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) may be raised
 - the most sensitive marker used for monitoring treatment efficacy and risk of relapse is AFP.
- Treatment of ovarian cancer:
 - Patients with low risk, early-stage ovarian cancer (stage I, grade 1 disease confined to one or both ovaries with an intact capsule and no ascites) after thorough surgical staging have a greater than 90% cure rate with surgery alone and close observation is required.
 - Platinum-based therapy, such as intravenous carboplatin and paclitaxel, is warranted for high risk, early-stage ovarian cancer (stage IC or II, grade 3 tumour or clear cell histology).
 - > Intraperitoneal chemotherapy is indicated for patients with stage III disease
 - Debulking surgery followed by chemotherapy is proven to be the best treatment option in patients with peritoneal carcinomatosis from ovarian cancer.
 - Intraperitoneal chemotherapy has less toxicity compared to IV chemotherapy and is better tolerated.
- A young man with a germ cell tumour (raised β-HCG) can expect a greater than 95% cure rate, especially with seminomas.
- β-HCG is the best tumour marker confers the best prognosis

Breast cancer

The triple assessment of a breast lump is essential to diagnose a breast lump accurately. It involves:

- 1. physical examination,
- 2. mammography and then
- 3. ultrasound guided fine needle aspiration (FNA).

Risk factors

- inherited BRCA-1 mutation (or BRCA-2)
 - the greatest risk
 - ➤ BRCA1/2 carriers have a 40–70% chance of getting <u>breast cancer</u> by age 70, and a 10–70% chance of getting <u>ovarian cancer</u> by age 70.
 - family history of breast cancer at a young age makes this more likely.
 - What is the DNA repair mechanism by which the BRCA1 and BRCA2 proteins act?
 - Double strand DNA break repair
 - BRCA involved in repair of double strand DNA breaks by homologous recombination.
- Early menarche
- · late menopause
 - due to increased hormone exposure throughout life.
- Nulliparity
- Oral contraceptive use is also associated with a slight increase in risk of developing breast and also endometrial cancer.

What is **the best predictive factor for local recurrence of breast cancer after** surgery, chemotherapy and radiotherapy?

- Age
 - Patients below the age of 40 are significantly more likely to develop local recurrence of a breast cancer than those aged 41+.

Screening

- · Mammograms screening
 - sensitive in older (because of less dense breast tissue)
 - ➤ not sensitive in younger (because of denser breast tissue) → MRI and ultrasound are better in them.
 - In young patients with a BRCA mutation, mammographic screening has a low sensitivity for detecting tumours
- Mammographic screening of all women between the ages of 50 and 70 years can reduce mortality from breast cancer by 25%. There is no evidence for routine screening below this age.
- mutation of BRCA1 or BRCA2 gene increases the risk of breast cancer → should be screened at younger than 50 years.

Breast MRI is used for patients with invasive breast cancer in the following circumstances:

- if there is a discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment
- if breast density precludes accurate mammographic assessment
- to assess tumour size if breast conserving surgery is being considered for invasive lobular cancer

metastatic spread.

Tumour marker

 CA15-3 tumour marker are used to assess disease activity in metastatic breast cancer

Staging CT is not used routinely in primary breast cancer, only if there is suspicion of

Management

- Breast-conserving therapy
 - lumpectomy with sentinel lymph node biopsy followed by breast irradiation
 - > indicated for patients with focal disease
 - randomised clinical trials have shown that the survival rate for women undergoing breast-conserving therapy is equivalent to that of those who undergo mastectomy,
 - breast-conserving therapy resulting in improved cosmetic outcomes and less morbidity than mastectomy.
 - Most patients treated with lumpectomy without radiation therapy have a high risk for local recurrence.
 - Sentinel lymph node biopsy is safe and adequate for screening the axillary lymph nodes for metastases in women with small breast tumours.
- Mastectomy
 - indicated in patients in whom complete excision cannot be achieved unless mastectomy is performed or radiation is contraindicated.
- Adjuvant radiotherapy is recommended by (NICE) given after wide local excision of a
 breast tumour to reduce the risk of local recurrence.
 - ➤ There is growing evidence that adjuvant radiotherapy also increases survival for those patients at high risk of relapse.
 - There is however a risk of increased cardiovascular mortality after 15-20 years, which may be reduced with the use of modern techniques such as conformal radiotherapy and intensity-modulated radiotherapy.
 - ➤ Wound healing can be reduced after radiotherapy, and a period of at least a few weeks is usually given between surgery and initiation of radiotherapy.
- Prophylactic mastectomy is indicated only in patients with BRCA1 or BRCA2.

Drug therapy

- Hormonal treatment is used to remove the proliferative stimulus of oestrogen from tumour cells.
- Tamoxifen is used for adjuvant hormone treatment in pre-menopausal women first line.
 - Tamoxifen acts by blocking the binding of oestrogen to its receptor within the nucleus.
 - In patients with oestrogen receptor-positive tumours, tamoxifen therapy for five years in addition to lumpectomy decreases the risk of a new breast cancer event.
 - long-term use is associated with:
 - vaginal bleeding,
 - endometrial thickening and increased risk of endometrial cancer

thromboembolism.

- ➤ The lack of oestrogen receptor staining suggests a poor response to hormonal therapy with tamoxifen.
- Anastrozole is used for adjuvant hormone treatment in post-menopausal women first line.

aromatase inhibitor

- Three aromatase inhibitors are licensed for treatment of early oestrogen-receptorpositive breast cancer:
 - 1. anastrozole.
 - 2. exemestane.
 - 3. letrozole.
- Aromatase inhibitors work by **preventing peripheral conversion of oestrogen** and therefore cause profound oestrogen deprivation in a post-menopausal woman.
- > This increases the risk of osteoporosis and fragility fractures.
- ➤ A DEXA scan must be done at the start of treatment to identify those patients in whom a bisphosphonate must be considered for bone protection.
 - Aromatase inhibitors can be continued in a patient who has suffered no fragility fractures providing adequate measures are taken for bone protection, for example, prescribing a bisphosphonate.
 - In patients who suffer a fragility fracture tamoxifen must be considered
 as this does have a partial oestrogen agonist action on bone, reducing the risk
 of osteoporosis.
- A common side-effect is **reduced bone mineral density**, and bone densitometry is therefore often carried out prior to and during treatment.
- ➤ Anastrozole is currently indicated for early oestrogen-receptor-positive breast carcinoma at a dose of 1 mg daily for 5 years.
- **Fulvestrant** is a new pure anti-oestrogen agent which appears to be as effective as anastrozole. It is given by sub-cutaneous injection once every three weeks.
 - ➤ mechanism of action → Selective oestrogen receptor down regulator
 - > has been shown to be equivalent to anastrazole in terms of efficacy.
 - Fulvestrant is the only endocrine agent currently available that can be given parenterally, which offers significant advantages to patients with swallowing difficulties.
 - > Fulvestrant is not currently given first line in post-menopausal women but this may change in the near future.
- The positive C-erb B2 (HER2/neu) staining suggests that trastuzumab (Herceptin) may be effective.
 - Several randomised trials have demonstrated that <u>52 weeks</u> of adjuvant trastuzumab therapy <u>reduces the risk for breast cancer recurrence</u> in women with HER2 overexpression by approximately <u>50%</u> and may even <u>reduce mortality by as much as 30%</u>.

- the best test for monitoring the patient while she is receiving Herceptin (trastuzumab)?
 - Three monthly echocardiogram
 - Herceptin appears to be directly toxic to the cardiac muscle itself with relative sparing of the electrical conductivity of the heart.
 - As such regular echocardiograms are the best test to assess treatment safety, a reduction of greater than 10% in ejection fraction indicating the need to stop treatment.
- Bisphosphonate therapy
 - prevents skeletal complications resulting from osteolytic bone involvement in patients with breast cancer.
 - An intravenous bisphosphonate (eg: zoledronic acid) is indicated for treatment of lytic bone metastases.
 - The evidence demonstrating benefit of oral bisphosphonate therapy such as alendronate in the treatment of bone metastases is conflicting.
- → oestrogen receptor (ER)-positive tumours + pre-menopausal women → Tamoxifen
- → oestrogen receptor (ER)-positive tumours + post-menopausal women → Anastrozole
- → ER-negative or are refractory to endocrine treatment → chemotherapy
- → Patients with HER2 overexpression → chemotherapy + trastuzumab.
- → patients with HER2-negative metastatic breast cancer → Bevacizumab

Prognosis

- Poor prognostic factors include:
 - high-grade tumour,
 - positive lymph node status,
 - > oestrogen-receptor-negative tumour,
 - progesterone-receptor-negative tumour,
 - young age (< 40 years),</p>
 - premenopausal at diagnosis
 - increased tumour size.

Paget's disease of the breast

- Overview
 - > Paget's disease of the breast is a rare (1-4% of breast cancers) form of breast cancer that affects the nipple and areola.
 - underlying invasive breast cancer, or ductal carcinoma in situ (DCIS) almost always present
 - unlike Paget's disease of the vulva
 - Malignant cells infiltrate into the epidermis via the mammary duct epithelium, leading to thickening of the affected skin.
- **Features**
 - > Presents with dermatitis or macular rash over nipple or areola
 - It presents insidiously and is similar in appearance to eczema; as such it often goes undiagnosed for several months.

Diagnosis

- Skin biopsy with immunohistochemistry is the first line investigation.
- Investigations should also be done for underlying malignancy:
 - biopsy if a lump is palpable,
 - imaging if no lump is palpable.
- Management
 - usually surgical with post-operative radiotherapy
- Prognosis
 - high chance of recurrence.

Radiotherapy

- External beam radiotherapy or use of targeted intraoperative radiotherapy does not render the patient radioactive. No radiation precautions need to be taken
- Use of brachytherapy methods can involve insertion of radioactive seeds or beads which may require some radiation protection precautions depending on the site.
- Use of an unsealed source, for example radio-iodine treatment of thyroid cancer, has substantial need for precautions and patients need to be isolated in a lead-lined side room, often for several days.

Chemotherapy

- Adjuvant chemotherapy is commonly given in many cancers to reduce the risk of local or distant recurrence or metastasis.
- multi-drug chemotherapy resistance
 - ➤ Upregulation of which protein is associated with multi-drug chemotherapy resistance? → P-glycoprotein
 - P-glycoprotein, which is also known as multidrug resistance protein 1, is a member of the adenosine triphosphate (ATP)-binding cassette transporters which actively remove harmful substances from the cytoplasm.
 - If upregulated these proteins can pump chemotherapeutic agents out of tumour cells leading to drug resistance.

Chemotherapy complications

- Oral mucositis
 - > Severe mucositis is common with head and neck cancer treatment due to the combination of chemotherapy and external beam radiotherapy.
 - Admit the patient for IV fluids and nutritional support
 - Often patients require a PEG or RIG to provide adequate nutritional support during their potentially curative treatment.
 - Oral hygiene is the mainstay of treatment in prevention of mucositis however it will not treat an existing mucositis.
 - Chlorhexidine mouthwash can improve a grade 1-2 mucositis.

Salivary Gland Tumors

- Most commonly occur in the parotid gland
 - > generally **benign**
 - if the tumor involves a non-parotid gland it is more likely to be malignant
- Types
 - pleomorphic adenoma
 - the most common benign salivary gland neoplasm.
 - ❖ 70% to 80% of all benign salivary gland tumours.
 - more common in **females** (middle-aged women > 40)
 - It is found mostly in the parotid gland (84%).
 - 90% of parotid gland pleomorphic adenomas arise lateral to the facial nerve.
 - benign with high rate of recurrence but may become malignant
 - Usually they do not enhance following intravenous contrast injection in CT.
 - The optimal treatment is superficial or total parotidectomy with facial nerve preservation
 - Warthin's tumor
 - benign
 - more common in males
 - heterotopic salivary gland tissue located in a lymph node
 - surrounded by lymphatic tissue
 - mucoepidermoid carcinoma
 - most common malignant tumor
 - note: muco = malignant
 - generally, involves parotid gland
 - combination of neoplastic mucus and squamous cells
- Physical exam
 - painless, moveable mass found at the angle of the jaw
 - pleomorphic adenoma
 - > disturbance in CN VII function
 - more likely to be malignant pleomorphic adenoma

Palliative care prescribing: pain

Metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

The breakthrough dose of short acting morphine should be 1/6th of the total 24-hour dose.

WHO recommendations

- Standard practice would be to follow the World Health Organization recommendations for the management of cancer pain, which suggest analgesia should be given:
 - > By the mouth that is, using the oral route for all drugs including morphine and other opioids unless patient is vomiting, semi-conscious, has dysphagia, etc.
 - By the clock persistent pain requires preventative treatment and as needed (prn) analgesia only is not acceptable.
 - By the ladder that is, the WHO analgesic ladder.
- The WHO analgesic ladder is as follows:
 - Step 1 Non-opioid +/- adjuvants (e.g. paracetamol/NSAIDs)

- Step 2 Weak opioid + non-opioid +/- adjuvants (e.g. co-codamol 30/500)
- > Step 3 Strong opioid + non-opioid +/- adjuvants (e.g. morphine, fentanyl, oxycodone).
- Nerve pain often also has a nociceptive opioid responsive element and hence opioids
 (with a combination of nonsteroidal anti-inflammatory drugs [NSAIDs]) should be
 tried first (eg: ibuprofen and tramadol) and used as part of the WHO analgesic ladder.
 Morphine would be tried next, followed by the other agents.

Starting morphine

- Morphine is the opioid of choice for treating moderate to severe cancer pain.
- Choices between morphine preparations
 - when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine(IR) (depending on patient preference), with oral immediate-release morphine for breakthrough pain
 - > oral modified-release morphine should be used in preference to transdermal patches
 - Immediate release preparations are used for titration as they offer greatest flexibility. Most patients should be started on 5-10mg orally every 4-hours, with the same dose prescribed as a breakthrough (or 'rescue') dose wherever needed. Once drug requirements are constant, the patient can be converted to modifiedrelease morphine.
 - Once a patient has been titrated on immediate release opioids these can be converted to the equivalent dose of a modified release preparation.
 - If a patient has good pain control on one drug, the modified release version of this drug should be used.

Morphine doses

- if no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required
- > When increasing the dose of opioids, the next dose should be increased by 30-50%.
- An appropriate starting dose of morphine sulphate immediate release (IR) should not be more than 10mg every 4 hours. Alternatively, morphine sulphate modified release (MR) 30mg 12 hourly could be used.
- Opioids Side effects:
 - Constipation: laxatives should be prescribed for all patients initiating strong opioids
 - Morphine causes constipation by enhancing intestinal ring contractions.
 This results in hypersegmentation which in turn impairs peristalsis.
 - 90% of patients taking morphine require a laxative and a stimulant is the best choice (such as senna). Senna is the most commonly used laxative for this indication
 - Nausea: patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered
 - drowsiness is usually transient if it does not settle then adjustment of the dose should be considered

Preferred opioids for patients with chronic kidney disease

Breakthrough dose = 1/6th of daily morphine dose

- Opioids should be used with caution in patients with chronic kidney disease.
 Alfentanil, buprenorphine and fentanyl are preferred
 - > Fentanyl patches are difficult to titrate because they are used for 72 hours. therefore, only used once a patient has a stable opiate usage.
 - Fentanyl is a selective µ receptor agonist.

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- It has extensive first-pass metabolism so is not especially effective orally.
- However, buccal absorption is good so lozenges are an effective mode of administration and have a rapid onset of action (five minutes). This is therefore very useful for patients with "breakthrough pain".
- It is very useful in renal failure as it is metabolised mainly in the liver and it has inactive metabolites.

What is the most appropriate opioid to prescribe for a syringe driver in renal failure?



Combination therapies antagonism

- Partial opioid agonists (for example, buprenorphine), when used in association with morphine, may produce a reduction in the analgesic effect due to partial antagonism.
- This is an aspect of pain management that needs to be considered when using combination therapies.

Oxycodone

- Oxycodone is often used as a <u>second line opioid</u> for patients who experience either inadequate analgesia or excessive side effects with morphine.
- It has similar analgesic properties to morphine but is twice as potent.
- It is available in immediate-release and modified- release oral preparations and can also be used parentally.
- Oxycodone can be used in moderate renal failure, but only as breakthrough pain relief.
 Modified release preparations should be avoided.
- Parental oxycodone is twice as potent as oral oxycodone.
- The total daily dose of immediate and modified release oral oxycodone is the same.
- causes less sedation, vomiting and pruritis than morphine but more constipation.

Opioid side-effects

Usually transient	Usually persistent
Nausea Drowsiness	Constipation

Conversion between opioids

 calculate the total daily dose of morphine salt, (include the doses of breakthrough pain) then convert it to the appropriate amount

From	То	Conversion factor
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 10

From	То	Conversion factor
Oral morphine	Oral oxycodone	Divide by 1.5-2**

^{**}historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

From	То	Conversion factor
Oral morphine	Subcutaneous morphine	Divide by 2
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5

Transdermal perparations:

The current BNF gives the following conversion factors for transdermal perparations

- transdermal fentanyl
 - a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily
 - > fentanyl 75 patch is equivalent to 180mg daily intake of morphine salt
 - > fentanyl 100patch is equivalent to 240mg daily morphine salt.
- · transdermal buprenorphine
 - transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

Diamorphine

- Diamorphine has a rapid onset so could be used for breakthrough pain <u>if the renal</u> <u>function is normal.</u>
- Constipation is a characteristic sequel to treatment
- · Hallucinations also tend to occur.
- An aperient (laxative) should always be added to the treatment regime.
- · Addiction is not a problem.
- An intramuscular injection is three times more effective than the same oral dose.
- the best option for controlling pain associated with vomiting in palliative care →
 Subcutaneous diamorphine by continuous infusion (able to effectively titrate the dose
 to achieve adequate analgesia)

Codeine

- The analgesic effect of codeine depends on its conversion to morphine by the CYP2D6 hepatic enzyme. Up to 10% of Caucasians are CYP2D6 poor metabolisers and are unlikely to derive any analgesia from it.
- If hepatic metabolise is impaired for any other reason (drugs or hepatic impairment) patients are also unlikely to benefit from codeine.

Methadone

- acts as a neuropathic agent by NMDA antagonism.
- Methadone can be used as a <u>third line</u> opioid for patients with complex pain that is poorly responsive to other opioids and adjuvants
- Opioids which are safe in CKD 4 and 5 include fentanyl, buprenorphine and methadone.

Incident pain

- defined as pain which comes on as a <u>result of an action or activity</u>, for example during personal care (pain throughout the day is otherwise well controlled).
- Treated with rapid onset and short-acting opioid such as:
 - Sublingual fentanyl
 - > morphine sulphate immediate release liquid.
 - A breakthrough dose (1/6th of the total daily dose) of morphine should be given 30 minutes prior to the activity as indicated in the BNF.

Other notes:

- Nifedipine
 - relieves painful oesophageal spasm and tenesmus associated with gastrointestinal tumours and could be used to relieve odvnophagia.
- Corticosteroids
 - used to treat pain from central nervous system tumours
- Oxybutynin
 - painful bladder spasm may be relieved by oxybutynin.
- Hyoscine
 - ➤ to reduce air way secretions in palliative care → Both hyoscine and atropine when given subcutaneously are thought to be equally appropriate for drying up secretions.
 - > hyoscine s/c can be given up to three times per day in boluses of 10-20 mg.

Cyclizine

- > Cyclizine is a commonly used antihistamine antiemetic and its primary site of action is the vomiting centre (which is rich in histamine and muscarinic cholinergic receptors).
- Cyclizine has a strong affinity for muscarinic receptors and therefore anticholinergic side effects (dry mouth, drowsiness, blurred vision, constipation, etc) are common, especially in the first few days.

Gabapentin

- ➤ **Gabapentin** is a commonly used adjunctive agent for neuropathic pain.
- mechanism of action: (Activation of GABA inhibitory system).
- > Four to six weeks of treatment are often needed before the patient experiences benefit.

Bisphosphonates

- inhibits osteoclastic bone resorption
- > useful for bone pain and the associated hypercalcaemia, especially in breast cancer and myeloma.
- Whilst bisphosphonates have a role in bone metastases they are not suitable for acute pain.
- The risk of osteonecrosis of the jaw is much greater for patients receiving intravenous bisphosphonates in the treatment of cancer.
 - All patients receiving bisphosphonates for cancer should have a dental checkup before bisphosphonate treatment.
 - other patients who are prescribed bisphosphonates should have a dental examination only if they have poor dental health.
- > The beneficial effect of bisphosphonates can be delayed for up to two weeks and can last for one month, and treatments are therefore usually given monthly (typically for 6 months).
- > increase analgesia while waiting for the bisphosphonates to work and review over the next few days to see whether you could reduce them again.

Acupuncture is playing an increasing role in pain management. Which structures are involved in mediating the effects of acupuncture? Cerebral cortex and A beta nerve fibres.

- The A beta nerve fibres are the path for fast transmission of sensation.
- Acupuncture also has a central effect.

Opioid toxicity in palliative care

most opiates are renally excreted, leading to opiate toxicity. Fentanyl, buprenorphine and methadone are metabolised by the liver and are therefore safer in renal failure

Transdermal fentanyl absorption is increased by heat (e.g. hot water bottle) or pyrexia, potentially leading to opioid toxicity

- May be precipitated by:
 - > Renal impairment with renally excreted opiates
 - increase transdermal fentanyl absorption by heat eg: fever
 - reduction in opioid requirement. This is a common occurrence in patients who have radiotherapy for bone metastases if their medication dose is not adjusted.
- Features:
 - Reduced conscious level, hallucinations, vomiting, myoclonic jerks and pinpoint pupils.
- Management
 - stop the long acting opioid temporarily to allow the excess drug to be excreted and then rely on short acting opioid for any breakthrough pain that might occur.
 - once the patient recovered, the long acting opioid can be reintroduced at a much-reduced dose.
 - Although the patient is opioid toxic, giving naloxone would not usually be the right thing to do.
 - Naloxone antagonises opioid receptors in the nervous system and this can cause patients significant pain and distress as their analgesia is reversed.
 - Unless the patient is in a peri-arrest situation where use of naloxone could be justified, it is better simply to withdraw the regular opioid until the patient recovers

Palliative care prescribing: nausea and vomiting

Opiate induced nausea

- Haloperidol
 - > 90% of patients taking morphine require antiemetics (morphine stimulates D2 receptors in the CTZ).
 - Haloperidol is the first-choice antiemetic for opiate induced nausea in the palliative care setting.
 - ➤ Haloperidol acts as a central dopamine (D2-receptor) antagonist. The chemoreceptor trigger zone (CTZ) is rich in dopaminergic receptors. Opioid related nausea is thought to be predominantly due to dopamine pathways in the CTZ.
 - haloperidol → dopamine receptor antagonist (D2) activity → drug-induced parkinsonism (DIP).

Post-chemotherapy or radiotherapy induced nausea

- Ondansetron (5HT₃ antagonist) is mainly used in post-chemotherapy or radiotherapy induced nausea.
- In UK 5HT₃ antagonists are licensed only for post-chemotherapy and post-operative nausea.
- Which antiemetics is most useful following treatment with a platinum-based chemotherapy? → Ondansetron
 - Examples of platinum-based chemotherapies are cisplatin, carboplatin and oxaliplatin

Nausea associated with cerebral disease (brain metastases)

- If he patient's history raises the possibility of <u>brain metastases</u>, cyclizine would be the most appropriate first line agent.
 - > It targets the dopamine and cholinergic receptors and is widely accepted as the best antiemetic for nausea associated with cerebral disease.

Treatment of vomiting associated with breast cancer chemotherapy

- modern palliative chemotherapy for breast cancer would be unlikely to cause severe nausea and vomiting.
- The patient may have anticipatory vomiting (before attending for treatment) almost certainly associated with anxiety about chemotherapy. Therefore, treatment with a benzodiazepine as an anxiolytic as well as an antiemetic would be the most logical.

Palliative care prescribing: hiccups

Hiccups in palliative care - chlorpromazine or haloperidol

Management of hiccups

- Metoclopramide is the first choice to treat hiccup as well as nausea.
- chlorpromazine is licensed for the treatment of intractable hiccups
- Other options include: baclofen, nifedipine, haloperidol, gabapentin
- dexamethasone is also used, particularly if there are hepatic lesions
 - In the presence of hepatic or cerebral cancer a trial of dexamethasone may induce some remission

Palliative care prescribing: Constipation

Causes

- Constipation is common in patients with advanced cancer, particularly in those taking opioid medication, with reduced oral intake and reduced mobility.
- Hypercalcaemia can cause constipation (a constipation in cancer → do blood tests, including bone profile)
 - > Hypercalcaemia is a common problem in palliative care.
 - prostate cancer with bone metastasis is a frequent cause.

Treatment

- Polyethylene glycol (Movicol) would seem the best choice in this scenario.
 - It has an osmotic action and helps to retain water in the gut to aid faecal passage.
 - It is generally better tolerated than some other oral laxatives and has been shown to be more effective than lactulose in the management of chronic constipation.
- Lactulose (an osmotic laxative) is usually avoided in palliative care
 - > as it can cause abdominal cramps and excessive flatulence.
 - Its sweet taste can be unpalatable for some patients
 - > it needs to be consumed with large volumes of liquid which is sometimes not practical for palliative care patients.
- Co-danthramer is a combination of danthron (a stimulant laxative) and poloxamer (a stool softener) and is a popular choice for constipation in palliative care. It is <u>licensed only for use in patients with a terminal illness</u> and should not be given to those who are incontinent (of urine or faeces) due to the risk of developing a 'danthron burn' through prolonged contact with the skin.

Palliative care prescribing: agitation and confusion

Causes

- hypercalcaemia,
- infection.
- urinary retention
 - > can even develop in patients who have not received any hydration for several days.
 - Assessment for catheterisation should be one of the first management steps in a newly agitated patient.
- · medication.

Management

- Treatment of underlying cause
- If specific treatments fail, then the following may be tried:
 - > first choice: haloperidol
 - > other options: chlorpromazine, levomepromazine
 - > Terminal agitation
 - In the terminal phase of the illness then agitation or restlessness is best treated with midazolam
 - <u>Midazolam</u> is the drug suggested by the Liverpool Care Pathway (LCP) (starting dose of 2.5 - 5 mg sc PRN).
 - benzodiazepines are traditionally the first line for terminal agitation.

Palliative care: Breathlessness

Opioids are the first line treatment to reduce the sensation of breathlessness in Palliative care

- Breathlessness is a significant problem in the palliative care setting and not just in patients with lung cancer.
- Palliation of breathlessness involves:
 - First-line: Opioids
 - Opioids are very effective agents to reduce the sensation of breathlessness - they reduce inappropriate respiratory drive.
 - They rarely cause respiratory depression when used correctly.
 - > Second line: <u>Benzodiazepines</u> (effective agents after opioids).
 - > Other therapies
 - Psychological support and physiotherapy
 - are very useful adjuncts to medications.
 - However, these <u>take time</u> and if the patient is distressed, they are not helpful in the immediate cases (unless breathing techniques have been taught).
 - Oxygen
 - has a small role in the management of breathlessness in palliative medicine, unless the patient is hypoxic.
 - It can be necessary when patients become psychologically dependent on supplementary oxygen.

Palliative care: end of life care

- Glucocorticoids are prominent in end of life care
 - Benefits of steroids
 - Improve general feelings of wellbeing
 - Relive fatigue and improve energy
 - Relive nausea
 - Control of pain
 - 15% improvement in pain
 - ❖ If the patient is unable to obtain satisfactory pain relief despite an escalating opiate regimen → Commence trial with dexamethasone
 - One of the sources of pain associated with liver metastases is due to stretching and irritation of the liver capsule for which a trial of dexamethasone may provide an analgesic effect.
 - Liver capsule pain tends not to be opioid responsive, therefore increasing the modified or immediate release morphine would not be the correct option.
 - Dexamethasone is the usual agent of choice
- The most important aspect of management is to try to keep the patient calm and relieve distress with a large dose of midazolam (10mg).
 - In a massive terminal haemorrhage, a large dose of midazolam (10mg) can be given as part of 'crisis management' to relieve distress. Red or green towels or blankets should be available to soak up and mask the colour of blood

Epstein-Barr virus: associated conditions

EBV: associated malignancies:

- Burkitt's lymphoma
- Hodgkin's lymphoma
- nasopharyngeal carcinoma
- Epstein-Barr virus infects B lymphocytes and squamous epithelial cells of the oropharynx. The virus can transform B cells and epithelial cells to produce tumors
- Malignancies associated with EBV infection
 - Burkitt's lymphoma (both African and sporadic Burkitt's)
 - > Hodgkin's lymphoma
 - nasopharyngeal carcinoma
 - Epstein-Barr virus is detectable in over 90% of nasopharyngeal cancers
 - the most common type is the undifferentiated form.
 - > HIV-associated central nervous system lymphomas
- The non-malignant condition hairy leukoplakia is also associated with EBV infection.

September 2019 exam: What type of virus family is associated with nasopharyngeal carcinoma? Herpesvirus (Epstein-Barr virus is one of the herpes viruses)

T cell lymphoma (Adult T-cell lymphoma (ATLL)

- makes up about 10-20% of non-Hodgkin's lymphomas
- has a worse prognosis than B cell lymphoma.
- Adult T-cell leukaemia/lymphoma (ATLL) is a potentially aggressive type of mature T-cell non-Hodgkin lymphoma.
- It is linked to the viral infection, HTLV-1 (human T-cell lymphotropic virus 1).
- It is more prevalent in countries where infection with HTLV-1 is common, such as Japan, China, the Caribbean, South and Central America and West Africa.
- ATLL occurs in 2%-5% of people who are infected with the HTLV-1 virus.
- The HTLV-1 virus is a retrovirus, and is in the same class of virus as the HIV/AIDS virus. It
 is believed that the HTLV-1 virus is a key factor in the development of this rare lymphoma
 which is transmitted through sexual contact, exposure to contaminated blood or
 breastfeeding.
- · slightly more common in men than in women,
- In acute ATLL, symptoms develop rapidly and include:
 - fatigue,
 - skin rash
 - enlarged lymph nodes
 - hypercalcaemia may also be present which can cause confusion, bone pain and severe constipation.
- lymphomatous form of ATLL presents with:
 - enlarged lymph nodes.
- Chronic ATLL is slow growing and frequently characterised by:
 - enlarged lymph nodes
 - Skin rash and
 - fatigue.
- Smouldering ATLL develops slowly and presents with very mild symptoms such as a few lesions on the skin.
- Patients with the chronic or smouldering types of ATLL can progress to the acute form in about 25% of cases.
- for the acute and lymphomatous types: Therapies include antiviral drugs, such as acyclovir and interferon, together with chemotherapy regimens

Testicular cancer

The triad of a testicular lump, a mass on chest X-ray and a raised (3-HCG (human chorionic gonadotrophin) are suggestive of testicular seminoma

Testicular mass

- ↑ LDH → pure seminomas germ cell tumor
- ↑ AFP → mixed non-seminomatous germ cell tumour

Epidemiology

Most common solid malignant tumor in young men in the US

Classification:

- germ cell tumors (comprise more than 90% of all tumours and more commonly malignant)
 - Germ cell tumours are classified as either:
 - pure seminomas

- seminoma is the most common type of testicular germ cell tumor.
- **❖** ~ 40%
- Good radiosensitivity; slow growth, late metastases, and better overall prognosis compared to nonseminomas
- Lactate dehydrogenase (LDH) is most likely to be elevated (in 40– 60%)
- ❖ A raised (3-HCG is found in around 15% of seminomas
- Orchidectomy with chemotherapy is curative in 90% of cases
- ❖ (3-HCG) levels may be a useful correlate with response to treatment
- mixed non-seminomatous germ cell tumours (NSGCTs)
 - Elevated AFP levels are most consistent with NSGCT
 - Choriocarcinoma is the most aggressive of the NSGCTs.
 - ⇒ Highly malignant and most aggressive
 - ⇒ Early hematogenous metastasis to the lungs or brain is common.
 - Most testicular GCTs cause scrotal swelling, with a palpable mass, choriocarcinoma is different in that the local tumour may be small or nonpalpable.
 - ⇒ Beta-human chorionic gonadotropin (Beta-HCG) is usually markedly elevated in pure choriocarcinoma but is only elevated in 10-15% of seminomas.
 - ⇒ Gynecomastia occurs due to elevation of beta-hCG levels and is therefore common in choriocarcinoma, but only rarely seen in patients with a seminoma.
 - On ultrasound scanning, choriocarcinoma is associated with haemorrhage and necrosis and may appear more cystic, inhomogeneous, and calcified than a seminoma. Calcifications and cystic areas are less common in seminomas than in nonseminomatous tumours.
- can cause precocious puberty in boys.
- Young men are more at risk for germ cell tumors.
- <u>teratoma</u> is a testicular germ cell tumor that is benign in children and malignant in adults.
- Non-germ cell tumors (make up less than 10% of all testicular tumours)
 - Levdig cell tumours
 - golden brown color on morphology
 - Eosinophilic cytoplasmic inclusion bodies called Reinke crystals are found in Leydig cell type of testicular tumors.
 - Sertoli cell tumours,
 - gonadoblastomas.
- <u>Testicular lymphoma</u> is the most common testicular tumor in **older men**.
 - Most common testicular tumor in men > 60 years of age
 - <u>Testicular lymphoma</u> is a cancer that arises from metastasis from metastatic lymphoma to the testes.
 - Usually extranodal non-Hodgkin lymphoma

Risk factors

- Cryptorchidism
 - Patients with history of cryptorchidism have a 10- to 40-times increased risk of testicular cancer
 - this risk is greater for the abdominal versus inquinal location of undescended testis.
 - Orchidopexy does not reduce the risk of subsequently developing a malignancy.
 - An abdominal testis is more likely to be seminoma, while a testis surgically brought to the scrotum by orchiopexy is more likely to be non-seminomatous germ cell tumours (NSGCTs)N.

- family history
- infertility
- Klinefelter syndrome, Down syndrome (increased risk for germ cell tumors)

Features

- testicular mass
 - Most commonly presents as a <u>hard, painless nodule on one testis</u> noticed by the patient or at a regular clinic examination.
- fatigue, weight loss,
- gynaecomastia
 - Rarely gynaecomastia can be the trigger by which a young man will seek medical attention; testicular examination should therefore be done in every case.
 - What is the mechanism by which patients with testicular cancer develop gynaecomastia?
 - → Raised oestrogen levels
 - testicular cancers → ↑β-HCG → ↑oestrogen → stimulates hypertrophy of breast tissue.
- Testicular tumors metastasize early via the lymphatic system (drain to the para-aortic lymph nodes first) into the retroperitoneum, with the exception of early hematogenously metastasizing choriocarcinomas.

Until proven otherwise, a firm nodule on the testis should be considered cancer

Investigation

β-hCG may be elevated in patients with seminomatous or nonseminomatous tumours,

AFP is increased only in patients with nonseminomatous tumours.

- Ultrasound of the testis is 90% to 95% accurate in diagnosis.
- tumour markers
 - used for diagnosis and in monitoring the treatment response.
 - > β subunit of human chorionic gonadotropin (β-hCG):
 - may be elevated in patients with seminomatous or nonseminomatous tumours
 - α-fetoprotein (AFP):
 - increased only in patients with <u>nonseminomatous</u> tumours
 - Raised AFP in a boy with testicular swelling are highly suggestive of a yolk sac tumor.
 - placental ALP
 - increased in seminomas,
 - Lactate dehydrogenase (LDH)
 - LDH is elevated in 40–60% of men with testicular germ cell tumours
 - may be the only tumour marker which is elevated in some men with seminomas
 - It is neither sensitive nor specific as a marker for tumour recurrence, although the level at baseline does have prognostic value in men with advanced disease.
- Raised oestrogen levels
- transillumination test is negative in testicular germ cell tumors.

HCG is always elevated in cases of choriocarcinoma and sometimes in seminoma. AFP is always elevated in yolk sac tumors.

In mixed germ cell tumors, both AFP and HCG may be elevated.

If testicular tumor is suspected, the testis is removed and sent to pathology without prior trans-scrotal biopsy

Treatment

- Radical orchiectomy to confirm histological diagnosis is initial treatment in most cases.
- followed by additional staging studies such as a CT scan of the abdomen and pelvis and radiograph of the chest.
- In testicular cancer the <u>BEP</u> combination is used: <u>B</u>leomycin, <u>E</u>toposide and Cisplatin (<u>P</u>latinum).
 - > Etoposide
 - works by inhibiting topoisomerase II and causing DNA degradation.
 - Etoposide is also used in the treatment of small cell lung cancer, leukemias, and lymphomas.
 - adverse effects: myelosuppression and alopecia.

Prognosis

• ~95% cure is expected with treatment

The <u>rapid deterioration</u>, seen over the course of a few hours, is most suggestive of <u>haemorrhage into a metastasis</u>. Teratomas are well known to metastasise via haematogenous spread, including to liver, lung, bone and brain.

Laryngeal cancer

Treatment

- Initial therapy for stages I and II is radiation therapy or surgery.
 - > early-stage disease could receive curative therapy with surgery or radiation alone.
 - External beam radiation is the curative and function sparing treatment for patient who prefer not to lose his ability to speak and he is willing to stop smoking immediately.
- Chemotherapy is not necessary in patient who has local and potentially curable disease.
- In the setting of lymph node-positive or locally advanced disease, the benefit of concurrent chemoradiotherapy is recommended.
- Cetuximab is a monoclonal antibody and is effective when combined with radiation, it has been found to improve local control and overall survival rates.

Von Hippel-Lindau syndrome

Definition

• VHL syndrome is an **autosomal dominant** condition predisposing to neoplasia.

Aetiology

- due to an abnormality in the VHL gene located on short arm of chromosome 3
 - von-Hippel-Lindau= 3 words for chromosome 3.
- VHL gene normally act as a tumor suppressor gene
 - VHL gene normally is responsible for regulating the hypoxia-inducible factor (HIF), a transcription factor.
 - In patients with VHL, there is constitutive expression of HIF resulting in angiogenesis and cancer development.

Epidemiology

- it has over 90% penetrance by the age of 65.
- prevalence is 1 in 39,000.
- Mean age at presentation of 27 years.

Types

- Type 1 VHL is associated with tumours in eye, brain, spinal cord, kidney and pancreas.
- Type 2 is associated with phaeochromocytoma:

Features

- haemangioblastomas of the CNS (The most common presentation)
 - > retinal haemangiomas: vitreous haemorrhage
 - Retinal haemangioblastomas is the initial presentation in 40% of patients.
 - Annual ophthalmological exam for haemangioblastoma is the most appropriate screening investigation
 - cerebellar haemangiomas is another common initial presentation.
 - CNS haemangioblastomas tend to be infratentorial.
 - cerebellar haemangiomas secretes erythropoietin-like substance, leading to a secondary polycythaemia.
 - haemangioblastomas are typically not cancerous, but they can compress the brain and spinal cord resulting in headaches, vomiting, paralysis, and ataxia
- cysts in various organs (e.g., kidney, pancreas, liver)
 - renal cysts (premalignant)
 - ↑ risk of developing clear cell renal cell carcinoma.
 - Renal cell carcinoma (Clear cell) is the commonest cause of death (70% of patients having renal cysts and carcinomas by age of 60 years).
 - > extra-renal cysts: epididymal, pancreatic, hepatic
- phaeochromocytoma
 - occurs in 20% of patients, although the incidence is much higher in those with von Hippel Lindau type 2
- endolymphatic sac tumours

Diagnosis

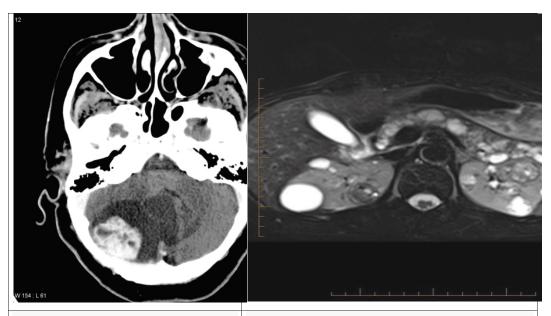
- genetic testing → mutations in the VHL gene.
 - ➤ Ideally, genetic testing in affected families should take place around the age of 5 years.

Treatment

- Asymptomatic small haemangioblastomas → observation.
- Renal cell carcinoma → surgery.

Monitorina

- · Affected individuals require:
 - yearly urinalysis, catecholamine screening, fluorescein angiography
 - 3-yearly brain magnetic resonance imaging.



CT scan showing a cerebellar haemangioma in a patient with Von Hippel-Lindau syndrome.

MRI showing renal cysts in patient with known Von Hippel-Lindau syndrome.

<u>Haemangiomas</u>

- Hemangiomas are benign vascular tumors that lead to a messy clump of dilated blood vessels.
- Hepatic hemangioma
 - ➤ a benign liver tumor composed of masses of blood vessels
 - > the most common benign tumor affecting the liver.
 - > The most common site of hemangiomas in internal organs is the liver.
 - > mesenchymal in origin and usually, are solitary
 - > oral contraceptives and steroids may accelerate the growth of a hemangioma.
 - Investigations
 - biopsies are contraindicated because of the risk of bleeding.
 - A good way to determine if a structure is hypervascular is to look for IV contrast enhancement.
- · Capillary hemangioma
 - > cherry hemangioma:
 - also known as (Campbell de Morgan spots)
 - benign capillary hemangioma of the elderly that does not regress
 - benign skin lesions which contain an abnormal proliferation of capillaries.
 - frequency increases with age.
 - The most common benign capillary skin tumor found in elderly
 - affect men and women equally.
 - Features
 - erythematous, papular lesions
 - typically 1-3 mm in size
 - non-blanching
 - not found on the mucous membranes
 - As they are benign no treatment is usually required.



- Infants with large hemangiomas should have <u>ultrasonography</u> of the abdomen to rule out the presence of other hemangiomas in the viscera.
- Propranolol is the first line of treatment of hemangiomas causing disfigurement.

Cytotoxic agents

The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

Alkylating agents

Cytotoxic	Mechanism of action	Adverse effects
Cyclophosphamide	Alkylating agent - causes cross-linking in DNA	Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma

Cytotoxic antibiotics

Cytotoxic	Mechanism of action	Adverse effects
Bleomycin	Degrades preformed DNA	Lung fibrosis
Doxorubicin	Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis	Cardiomyopathy

Antimetabolites

Cytotoxic	Mechanism of action	Adverse effects
Methotrexate	Inhibits dihydrofolate reductase and thymidylate synthesis	Myelosuppression, mucositis, liver fibrosis, lung fibrosis
Fluorouracil (5-FU)	Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)	Myelosuppression, mucositis, dermatitis
6- mercaptopurine	Purine analogue that is activated by HGPRTase, decreasing purine synthesis	Myelosuppression
Cytarabine	Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase	Myelosuppression, ataxia

Acts on microtubules

Cytotoxic	Mechanism of action	Adverse effects
Vincristine, vinblastine	Inhibits formation of microtubules	Vincristine: Peripheral neuropathy (reversible), paralytic ileus Vinblastine: myelosuppression
Docetaxel	Prevents microtubule depolymerisation & disassembly, decreasing free tubulin. has a further action in blocking bcl-2	Neutropaenia

Other cytotoxic drugs

Cytotoxic	Mechanism of action	Adverse effects
Cisplatin	Causes cross-linking in DNA	Ototoxicity, peripheral neuropathy, hypomagnesaemia
Hydroxyurea (hydroxycarba mide)	Inhibits ribonucleotide reductase, decreasing DNA synthesis	Myelosuppression

Vincristine - peripheral neuropathy

Busulfan

- · alkylating antineoplastic agent,
- Busulfan was the mainstay of the chemotherapeutic treatment of chronic myeloid leukemia (CML) until it was displaced by the new gold standard, imatinib
- Busulfan is used in pediatrics and adults in combination
 with cyclophosphamide or fludarabine/clofarabine as a conditioning agent prior to bone
 marrow transplantation, especially in chronic myelogenous leukemia (CML) and
 other leukemias, lymphomas, and myeloproliferative disorders.
- Busulfan lung
 - <u>Busulfan lung</u> is a form of drug-induced pulmonary toxicity with an idiopathic pulmonary fibrosis-like picture.
 - ➤ It is clinically symptomatic in 5% of patients.
 - There are no predictors of toxicity and pulmonary function testing is not a useful "screening" test.
 - Withdrawal of busulfan is the key step in treatment.

Combinations of chemotherapeutic agents

- what is the rationale behind using combinations of chemotherapeutic agents rather than single agents?
 - → Combination therapy decreases the chances of drug resistance developing
 - There are two main reasons for using combinations of different chemotherapy agents:
 - Different drugs will exert their effects through different mechanisms, so combining them will increase the number of tumour cells killed in each cycle.
 - 2. It also reduces the chances therefore of drug resistance developing.

Vinblastine

- Vinblastine is an M phase-specific chemotherapeutic agent that works by disrupting the assembly of microtubules via binding tubulin.
- Cell death results because anaphase cannot commence without the formation of the mitotic spindle and kinetochore.
- Which cellular event occurs in the same phase of the cell cycle at which vinblastine functions? → Breakdown of the nuclear membrane
- Breakdown of the nuclear membrane occurs during the prometaphase portion of mitosis.

Taxanes (e.g. Docetaxel) prevent microtubule disassembly

Cyclophosphamide

Cyclophosphamide - haemorrhagic cystitis - prevent with mesna

- Cyclophosphamide is an <u>alkylating agent</u> used in the management of cancer and autoimmune conditions.
- It works by causing cross-linking of DNA
- Cyclophosphamide is <u>inactive unless metabolised by the liver to 4-hydroxyl</u> <u>cyclophosphamide</u>, which decomposes into alkylating species as well as to chloroacetaldehyde and acrolein

Adverse effects

- haemorrhagic cystitis (Acrolein causes chemical cystitis):
 - > incidence reduced by the use of hydration and mesna
- myelosuppression
- transitional cell carcinoma
- · premature ovarian failure,
- infertility in both men and women.

Mesna

- 2-mercaptoethane sulfonate Na
- a metabolite of cyclophosphamide called acrolein is toxic to urothelium
- · mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

Cisplatin

Cisplatin may cause peripheral neuropathy

Cisplatin is associated with hypomagnesaemia

• Platinum-based antineoplastic (end with: -platin)

Mechanism of action

 Causes crosslinking in DNA → makes it impossible for rapidly dividing cells to duplicate their DNA for mitosis.

Side effects

- Marrow toxicity
- Ototoxicity
 - > Due to vestibulocochlear nerve damage (CNVIII)
 - Sodium Thiosulfate Prevents Cisplatin-Induced Hearing Loss in Children With Cancer
- Peripheral neuropathy
- Nephrotoxicity
 - The nephrotoxicity of platinum-class drugs seems to be related to reactive oxygen species
 - Hypocalcaemia, hypomagnesaemia and hypokalaemia may occur as a result of nephrotoxicity
 - > Amifostine is an antidote for cisplatin treatment to counteract nephrotoxicity.
 - > Adequate hydration and diuresis is used to prevent renal damage.
 - Chloride diuresis is a renal procedure that can be performed to prevent the nephrotoxicity caused by cisplatin.
- Alopecia,
- · Changes in taste.
- Although optic neuritis is described it is not a typical side effect.

Trastuzumab

Trastuzumab (Herceptin) - cardiac toxicity is common

A baseline echocardiogram to assess heart function is recommended prior to starting trastuzumab.

- Trastuzumab (Herceptin) is a monoclonal antibody directed against the HER2/neu receptor.
- It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab.

Adverse effects

- flu-like symptoms and diarrhoea are common
- cardiotoxicity: associated with Dilated cardiomyopathy in 2% to 7% of users
 - more common when anthracyclines have also been used(eg: Doxorubicin).
 - Toxic to cardiac muscle itself with relative sparing of the electrical conductivity of the heart
 - Studies have shown that activation of Erb-b2 (also known as HER-2), the receptor blocked by trastuzumab (Herceptin), is important in preventing the development of cardiomyopathy
 - Mechanism
 - Anthracyclines → activate stress signal pathways within the heart → cardiac damage
 - HER2 activation is protective against the damage that this stress signaling induces
 - HER2 inhibition removes this layer of protection, leading to → dilated cardiomyopathy.
 - > An echo is usually performed before starting treatment
 - Regular echocardiogram (three monthly) is the best test to assess treatment safety
 - Reduction of greater than 10% in ejection fraction indicating the need to stop treatment.

In which chemotherapeutic agents is the cumulative dose limited due to cardiotoxicity?

- > anthracycline chemotherapeutic agents (eg: Epirubicin)
 - Epirubicin and the other anthracycline chemotherapeutic agents are extremely potent but are limited by dose constraints.
 - Cumulative doses of over 900 mg/m2 can lead to significant cardiac toxicity and heart failure.
 - Trastuzumab can cause direct myocardial damage and must be monitored with regular echocardiograms but it is not limited to a maximum lifetime dose.

Erlotinib

- Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase (which is required for the conformational change) and binds in a reversible fashion to the adenosine triphosphate binding site.
- For the signal to be transmitted, two members of the EGFR family need to come together to
 form a homodimer. These then use the molecule of adenosine triphosphate (ATP) to
 autophosphorylate each other, which causes a conformational change in their intracellular
 structure, exposing a further binding site for binding proteins that cause a signal cascade to

the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped.

A key issue with EGFR-directed treatments is that after a period of 8-12 months, the
cancer cells become resistant to the treatment. This most commonly occurs due to a
mutation in the ATP binding pocket of the EGFR kinase domain. This prevents the
binding of erlotinib (Tarceva).

Imatinib

- Belong to the class of → Signal transduction inhibitor
- Imatinib is a **tyrosine kinase inhibitor** which is fairly specific for the bcr/abl protein. It blocks the active site, which has a number of downstream effects.
 - ➤ The result is reduced cell proliferation, reduced cell motility, decreased adhesion and increased apoptosis.
- Indications
 - accelerated or blast crisis phase of CML.
 - gastrointestinal stromal tumours.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor positive breast cancer

Adverse effects

- · menstrual disturbance: vaginal bleeding, amenorrhoea
- · hot flushes
- · venous thromboembolism
 - Particularly during and immediately after major surgery or periods of immobility
- endometrial cancer

Tamoxifen is typically used for 5 years following removal of the tumour.

Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

UK licensed monoclonal antibodies

Name	Target	Licensed indication
Infliximab	TNF-α	Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis
Palivizumab	F protein on RSV	Prophylaxis, RSV in premature infants or brochopulmonary dysplasia
Abciximab	Platelet glycoprotein IIb/IIIa	High risk coronary intervention
Rituximab	CD20	Refractory low grade or follicular B cell lymphoma
Basiliximab	IL-2 receptor α chain	Prophylaxis of acute rejection in allogeneic renal transplantation
Daclizumab	IL-2 receptor α	As Basiliximab
Trastuzumab	HER 2 growth receptor	Relapsed HER2 (high) breast malignancy

IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.

Rituximab

- Rituximab binds to CD20, an antigen located on pre-B and mature B-lymphocytes
- The receptor is thought to mediate B-cell lysis and apoptosis
- After rituximab therapy, levels of B-lymphocytes appear suppressed for around 6 months, with levels slowly increasing after this time
- As well as for rheumatoid arthritis, rituximab is also used for the treatment of non-Hodgkin's lymphoma
- Infusion reactions associated with cytokine release occur in up to 15% of patients receiving rituximab, and the medicine is administered in a specialist centre for this reason

Cetuximab

- Action → epidermal growth factor receptor (EGFR) inhibitor
 - > Cetuximab works by blocking the extracellular domain of EGFR preventing ligand binding and therefore preventing downstream signal transduction.
- . Cetuximab is a monoclonal antibody given by intravenous infusion
- The patient's tumour must express k-ras wild-type as k-ras mutated is constitutively active regardless of whether a ligand is attached or not.
 - Which histopathological subtypes is essential for successful treatment with cetuximab?
 - K-ras wild-type
 - Cetuximab and other EGFR inhibitors only work on tumors in which Kras is not mutated
 - it has no effect in colorectal tumors with a K-ras mutation (this also applied to the EGFR antibody panitumumab).
 - genetic testing to confirm the absence of K-ras mutations (and so the presence of the K-ras wild-type gene), is now clinically routine before the start of treatment with EGFR inhibitors.
- Cetuximab is licensed by NICE in metastatic colorectal cancer for k-ras wild-type proven
 patients who require downstaging prior to surgical resection of liver metastatic disease.
 - > 75% of patients with metastatic colorectal cancer have an **EGFR-expressing tumor** and are therefore considered eligible for treatment with cetuximab or panitumumab
- Side effect
 - acne type rash (the most important and serious SE).

Capecitabine

- Capecitabine is the oral analog of 5-fluorouracil, a chemotherapeutic agent which is broken down, predominantly, by dihydropyrimidine dehydrogenase (DPD).
- Deficiency of dihydropyrimidine dehydrogenase (DPD) is autosomal recessive and will lead to a toxin buildup which in homozygous patients is usually fatal.

Capecitabine versus 5-fluorouracil (5-FU)

- Advantages of capecitabine versus 5-fluorouracil (5-FU) → Can be orally administered
 - The major difference between capecitabine and 5-FU is that capecitabine is an oral prodrug of 5-FU.
 - > 5-FU is one of the most effective chemotherapeutic agents used in the treatment of advanced colorectal cancer, it is administered via IV infusion.
 - > Capecitabine is orally administered chemotherapy, it is then metabolised to 5-FU.
 - ➤ The final step in metabolism to 5-FU is thymidine phosphorylase, higher activity of thymidine phosphorylase occurring in tumour tissues.
- Evidence suggests that efficacy of capecitabine versus 5-FU is broadly similar,

Chemotherapy side-effects: nausea and vomiting

- Nausea and vomiting are common side-effects of chemotherapy.
- Risk factors for the development of symptoms include:
 - anxiety
 - > age less than 50 years old
 - > concurrent use of opioids
 - > the type of chemotherapy used
- For patients at low-risk of symptoms then drugs such as metoclopramide may be used firstline
- For high-risk patients, then 5HT3 receptor antagonists such as ondansetron are often
 effective, especially if combined with dexamethasone

Adverse effects of other cancer treatment

Purine analogue (eg: fludarabine) for CLL → Pneumocyscis jirovecii infection

- This cytotoxic agent affects T-cell function. Patients are therefore prone to opportunistic infections including pneumocystis infection.
- Patients therefore receiving purine analogues should also receive co-trimoxazole to reduce this risk
- All patients who receive purine analogues are at risk of transfusion-associated graft-versus-host disease and therefore should receive irradiated blood products. The clinical features of transfusion associated graft-versus-host disease are:
 - 1. pancytopaenia,
 - 2. liver dysfunction.
 - 3. diarrhoea and
 - 4. rash

Etoposide → secondary haematological malignancy

- In patients who have received Etoposide, secondary haematological malignancy may develop in as little as 1-3 years.
- It is currently indicated for the treatment of small cell lung cancer and non-seminomatous testicular carcinoma.

Filgrastim

- Action
 - granulocyte colony-stimulating factor (G-CSF)
- Mechanism
 - Filgrastim is similar to naturally occurring granulocyte colony-stimulating factor (G-CSF).
 - > produced by recombinant DNA technology using genetic material of Escherichia coli.
 - > stimulating the bone marrow to increase production of neutrophils.
- Indications
 - used to treat neutropenia caused by:
 - chemotherapy,
 - radiation poisoning,
 - congenital neutropenia
 - aplastic anemia
 - also used to increase white blood cells for gathering during leukapheresis.
- It is given either by injection into a vein or under the skin.
- side effects
 - > The most commonly observed adverse effect is mild bone pain after repeated administration and local skin reactions at the site of injection
 - > Severe side effects include splenic rupture and allergic reactions.
 - Other side effects include

- serious allergic reactions (including a rash over the whole body, shortness of breath, wheezing, dizziness, swelling around the mouth or eyes, fast pulse, and sweating),
- alveolar hemorrhage, acute respiratory distress syndrome, and hemoptysis.
- Severe sickle cell crises, in patients with sickle cell disorders.

Sargramostim

- Action
 - granulocyte macrophage colony-stimulating factor (GM-CSF)
- It is produced in yeast
- · stimulate other myeloid and megakaryocyte
- Indications
 - for myeloid reconstitution after bone marrow transplantation.
 - neutropenia induced by chemotherapy
- side effects
 - GM-CSF can cause more severe effects, including fever, arthralgias, and capillary damage with edema.
 - > edema



Third edition

Notes & Notes

For MRCP

Volume 3

By

Dr. Yousif Abdallah Hamad

Updated 2022



Foreword

With the grace of the Almighty Allah, I have introduced the third edition of the popular book, the Notes & Notes for MRCP Part & 2.

The MRCP exam requires a wide range of information, particular thinking, and question directed experience.

This book is directed mainly at those who need comprehensive revision of the topics which commonly appear in the written MRCP exams.

It will be helpful to go through these topics before you start solving the best of the five questions; it is also recommended to go quickly over this book in the last few weeks before the day of your exam.

This new edition contains the new published guidelines.

I hope you will find the maximum benefits from this book to get through MRCP written exams.

To practice the best of five questions we advise you to join the best website for MRCP passonexam.com

For any enquiry or comment, please do not hesitate to contact me.

"The mind is not a vessel to be filled, but a fire to be kindled." — **Plutarch.**

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The 10 Golden Tips for MRCP written exams you will ever need

- 1. For MRCP, do not read hard; read smart.
- 2. Three to six months is usually enough for preparation.
- 3. Practice the best of the five questions as much as possible.
- 4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
- 5. Remember, you are getting ideas and concepts from the questions.
- 6. Time factor in the exam room is the leading killer after poor preparation.
- 7. Manage your time wisely.
- 8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
- Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
- 10. Practice, practice and practice.



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Red eye

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Third edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Rheumatology

Updated 2022

Bone markers

Bone remodeling

- Cells involved
 - ⇒ Osteoclasts: degrade bone tissue by secreting collagenase and H+
 - ⇒ Osteoblasts:
 - Build bone tissue by secreting type I collagen
 - Activity assessed by an increase in bone ALP, osteocalcin, and type I procollagen propeptides

Bone markers are useful for:

- · prediction of prognosis
- · prediction of fracture risk
- · assessing suitability for therapy and
- · monitoring the success of therapy.

Markers of bone formation	Markers of bone resorption
(measured in serum)	(measurable in serum or urine)
Bone-derived alkaline	Telopeptides
phosphatase (ALP).	Pyridinium cross-linking molecules
Osteocalcin	Tartrate-resistant acid phosphatase
 Procollagen type 1 propeptides. 	(TRAP)
	Hydroxyproline.

Rheumatoid factor

Rheumatoid factor is an IgM antibody against IgG

Overview

- Rheumatoid factor (RF) is a circulating antibody (usually IgM) which reacts with the Fc portion of the patients own IgG.
- Rheumatoid factor is an antibody with reactivity to the heavy chain of IgG.
- The rheumatoid factor may be of IgM, IgG or IgA class.
- The conventional (agglutination) test, detects only IgM RF.
- high titre levels are associated with severe progressive disease (but NOT a marker of disease activity).

A positive rheumatoid factor is associated with:

- More severe erosive disease
- Extra-articular manifestations including subcutaneous nodules and
- Increased mortality.

Conditions associated with a positive RF include:

- Sjogren's syndrome (around 100%)
- Felty's syndrome (around 100%)
- Mixed cryoglobulinemia (types II and III) 40 to 100%

- rheumatoid arthritis (70-80%)
- Mixed connective tissue disease 50 to 60%
- infective endocarditis (= 50%)
- SLE (= 20-30%)
- systemic sclerosis (= 30%)
- Polymyositis/dermatomyositis 5 to 10%
- general population (= 5%)

Rheumatoid arthritis

Rheumatoid arthritis - HLA DR4

Rheumatoid arthritis - TNF is key in pathophysiology

- Around 70% of patients with rheumatoid arthritis are HLA-DR4.
- Patients with Felty's syndrome (a triad of rheumatoid arthritis, splenomegaly and neutropaenia) are even more strongly associated with 90% being HLA-DR4

Epidemiology

- Prevalence = 1%
- F:M ratio = 3:1
- Peak onset = 30-50 years, although occurs in all age groups

Aetiology

- Idiopathic inflammatory autoimmune disorder of unknown etiology
- Genetic disposition: associated with HLA-DR4 and HLA-DR1

Pathophysiology

- Autoimmune inflammation induces formation of pannus (proliferative granulation tissue), which erodes articular cartilage and bone.
- Citrullinated proteins (converted from arginine to citrulline) are recognized as foreign →
 Activation and migration of CD4+ T cells to synovial joints → recruitment of macrophages
 → secretion of cytokines (TNF-α, IL-1, IL-6) → inflammation and proliferation → pannus
 and synovial hypertrophy → invasion, progressive destruction, and deterioration of cartilage
 and bone
- TNF is an important in the pathogenesis of rheumatoid arthritis.
- Rheumatoid factor (RF)
 - ⇒ Antibodies against Fc portion of IgG (rheumatoid factor, RF) are produced to aid in removing autoantibodies and immune complexes.
 - RF excess triggers formation of new immune complexes and type III hypersensitivity reaction
 - ⇒ Individuals with positive RF are more likely to develop extraarticular manifestations.

Rheumatoid arthritis - TNF is key in pathophysiology

Diagnosis

• The diagnosis of RA is clinical

- NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.
- Consider RA in patients with arthralgia, joint stiffness, and synovitis lasting ≥ 6 weeks

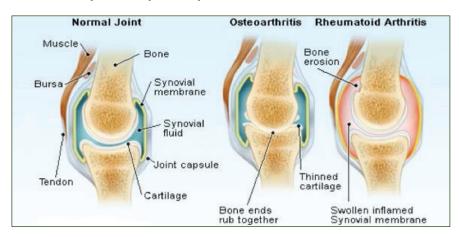
2010 American College of Rheumatology criteria

- Target population. Patients who:
 - 1) have at least 1 joint with definite clinical synovitis
 - 2) with the synovitis not better explained by another disease
- Classification criteria for rheumatoid arthritis (add score of categories A-D; a score of 6/10 is needed definite rheumatoid arthritis)

Factor	Scoring	
A. Joint involvement		
	1 large joint	0
	2 - 10 large joints	1
	1 - 3 small joints (with or without involvement of large joints)	2
	4 - 10 small joints (with or without involvement of large joints)	3
	10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)		
	Negative rheumatoid factor (RF) and negative anti-cyclic citrullinated peptide (Anti-CCP)	0
	Low-positive RF or low-positive Anti-CCP	2
	High-positive RF or high-positive Anti-CCP	3
C. Acute-phase reactants (at least 1 test result is needed for classification)		
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D. Duration of symptoms		
	< 6 weeks	0
	> 6 weeks	1

Articular manifestations

- Polyarthralgia
 - ⇒ Symmetrical pain and swelling of affected joints (also at rest)
 - ⇒ Frequently affected joints
 - Metacarpophalangeal (MCP) joints
 - Proximal interphalangeal (PIP) joints (DIP joints are NOT typically affected in RA.)
 - Wrist joints
- Morning stiffness (often > 30 min) that usually improves with activity
- Joint deformities
 - ⇒ **Swan neck deformity:** PIP hyperextension and DIP flexion
 - ⇒ **Boutonniere deformity:** PIP flexion and DIP hyperextension.
 - ➡ Hitchhiker thumb deformity (Z deformity of the thumb): hyperextension of the interphalangeal joint with fixed flexion of the MCP joint
 - ⇒ Ulnar deviation of the fingers
 - ⇒ Piano key sign: dorsal subluxation of the ulna
 - ➡ Atlanto-axial subluxation: A loss of ligamentous stability between the atlas (C1) and axis (C2), which can result in compression of the spinal cord, medulla, and/or vertebral arteries by the odontoid process, especially upon neck flexion. Most commonly caused by Down syndrome, rheumatoid arthritis, and trauma.



The earliest manifestation of rheumatoid arthritis in the feet \rightarrow swelling of the metatarsophalangeal joints

Extraarticular manifestations

- Constitutional symptoms: Low-grade fever, myalgie, malaise, fatigue, weight loss
- Rheumatoid nodules:
 - ⇒ Nontender, firm, subcutaneous swellings (2 mm–5 cm). Commonly occur in areas exposed to higher pressure, e.g., extensor side of the forearm, bony prominences
 - ⇒ Rheumatoid pulmonary nodules may be accompanied by fibrosis and pneumoconiosis (Caplan syndrome).
 ⇒
- Lunas:
 - ⇒ pleuritis, pleural effusions, interstitial lung disease (e.g., organizing pneumonia)
 - ⇒ rheumatoid pleural effusion: characterised by → low glucose level
 - ⇒ cricoarytenoid arthritis:

6 Chapter 8 Rheumatology

- seen in up to 75% of patients with RA
- It can cause stridor, but is often asymptomatic.
- symptoms can rapidly worsen in the <u>post-operative period</u>.
- the most helpful diagnostic test → Spirometry with flow-volume loop
- Patients can need urgent tracheostomy and steroids, both orally and via joint injection.
- Eye:
 - ⇒ keratoconjunctivitis sicca (dry eyes) (most common)
 - ⇒ scleritis, and episcleritis
- Endocrine and exocrine glands: secondary Sjogren syndrome
- Hematological
 - ⇒ Anemia of chronic disease (normocytic anemia)
 - NSAIDs and/or steroids → increased risk of GI bleeding → iron deficiency anemia (microcytic anemia)
 - $\blacksquare \quad \text{Methotrexate} \rightarrow \text{decreased folate level} \rightarrow \text{macrocytic anemia}$
 - ⇒ Neutropenia
 - ⇒ Splenomegaly
- Heart:
 - Pericarditis and myocarditis, constrictive <u>pericarditis</u> is the commonest cardiac complication of rheumatoid arthritis
 - ⇒ ↑↑ risk of myocardial infarction, stroke.
- Musculoskeletal: Tenosynovitis and bursitis, Carpal tunnel syndrome
- Vascular:
 - ⇒ Peripheral vasculitis, manifests as livedo reticularis
 - ⇒ Raynaud phenomenon

Investigations

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

- Specific parameters (serological studies)
 - ⇒ Anti-cyclic citrullinated peptide (Anti-CCP) antibodies
 - It has sensitivity similar to RF (70-80%) with a much higher specificity of 90-95%.
 - a prognostic marker.
 - ⇒ Rheumatoid factor (RF)
 - IgM autoantibodies against the Fc region of IgG antibodies
 - Present in 70–80% of patients, but not specific to RA
 - ⇒ Serological studies may be negative (i.e., seronegative RA): Up to 30% of patients with RA are negative for Anti-CCP and RF.
- Radiographic features
 - ⇒ X-ray of both hands and feet: initial test
 - Early findings : soft tissue swelling, osteopenia (juxta-articular)
 - Late findings: joint space narrowing, marginal erosions of cartilage and bone, osteopenia (generalized), subchondral cysts
- Typical RA findings on x-rays may be subtle or absent upon diagnosis in many patients with early RA; therefore, ultrasound or MRI may be more informative, as they have higher sensitivity for detecting early signs of inflammation and erosion.
- Analysis of synovial fluid
 - ⇒ Sterile specimen with leukocytosis (WBC count 5000–50,000/mcL)
 - **⇒** Abundant neutrophils.
 - ⇒ High protein levels.

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

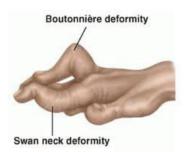
The radiographic features of rheumatoid arthritis can be remembered by the mnemonic LESS: Loss of joint space, Erosions, Soft tissue swelling, and Soft bones (osteopenia)

Early x-ray findings	Late x-ray findings	
 loss of joint space juxta-articular osteoporosis soft-tissue swelling 	periarticular erosionssubluxation	

Differential diagnosis

- Rheumatoid arthritis typically affects the metacarpophalangeal and proximal interphalangeal joints symmetrically. Psoriatic arthritis affects the distal interphalangeal joints and tends to be asymmetrical.
- Rheumatoid arthritis VS osteoarthritis

	Rheumatoid arthritis	Osteoarthritis
pathophysiology	autoimmune (inflammatory)	degenerative due to ↑ wear and tear on joints → loss of cartilage (non-inflammatory)
Age of starting	At any age	Usually later in life
Speed of onset	Rapid, over weeks to months	Slow, over yeas
Pain	improves with movement	worse with movement and better with rest
Primary joint affected	Proximal interphalangeal	Distal interphalangeal
	Metacarpophalangeal	Carpometacarpal
Heberdens nodes	Absent	Present
Joint characteristics	Soft, warm and tender	Hard and bony (little or no swelling)
Stiffness	Worse after resting (morning stiffness)	If present, worse after effort, may be described as evening stiffness
	Usually > 1 hour	Usually <1 hour
Systemic symptoms	Present (eg: fatigue)	Absent
RF and anti-CCP	Positive	Negative
ESR and C- reactive protein	Elevated	Normal
x-ray	Osteophytes absent	Osteophytes may be present





Referral

- Indications for urgent referral for specialist opinion: any person with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:
 - ⇒ the small joints of the hands or feet are affected
 - ⇒ more than one joint is affected
 - ⇒ there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

Prognosis: poor prognostic features:

- Anti-CCP antibodies (The poorest prognostic factor)
- · Rheumatoid factor positive
- HLA DR4
- Insidious onset: Acute or Sudden onset is not a poor prognosis.
- Poor functional status at presentation
- X-ray: early articular erosions (e.g. within the first 6 months of presentation and in less than
 2 years)
- Extra articular features e.g. nodules
- Female sex.

Rheumatoid arthritis: patients have an increased risk of IHD

Popliteal cysts ('Baker's cysts') may occur in rheumatoid arthritis following persistent effusion into the knee joint.

Which micro-organisms may be associated with the development of rheumatoid arthritis in susceptible patients? \rightarrow Proteus mirabilis

Felty's syndrome (RA + splenomegaly + low white cell count)

Poorly controlled rheumatoid arthritis + proteinuria and hypoalbuminaemia raises the possibility of systemic amyloidosis → Rectal biopsy

MRCPUK-part-1-September- 2009 exam: MRCPUK-part-1-jan-2018: Which (HLA) types is most associated with rheumatoid arthritis?

⇒ HLA DR4

A patient of RA on etanercept, scheduled for elective surgery. What advice regarding his medication should be given prior to surgery? → Stop etanercept 2–4 weeks prior to surgery

Updated British Society for Rheumatology (BSR) guidelines (January 2005) for prescribing tumour necrosis factor (TNF-α) blockers in adults with RA recommend:

- withholding etanercept and other TNF- blockers (infliximab and adalimumab) for 2–4 weeks prior to a major surgical procedure.
- restarted postoperatively if there is no evidence of infection and once wound healing is satisfactory.

Rheumatoid arthritis: Management

Approach

Acute anti-inflammatory treatment

- ⇒ Temporary (< 3 months) symptomatic treatment with glucocorticoids and/or NSAIDs is indicated for disease flares (i.e., episodes of increased disease activity and symptom worsening).
 </p>
- ⇒ Glucocorticoids (prednisone)
 - Short-term (i.e., < 3 months) therapy at the lowest effective dose is preferred.
 - Longer term therapy only used in patients with highly active RA who do not respond to maximum doses of DMARDs.
 - Glucocorticoids should be used at the lowest effective dose and only for short periods of time to reduce the risk of their many adverse effects (e.g., hypertension, osteoporosis, infections).
- ⇒ NSAIDs and selective COX-2 inhibitors: relieve symptoms, but do not improve the prognosis.

Long-term treatment

- ⇒ Initiation of treatment: all patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible.
- ⇒ Consider short-term concomitant use of acute anti-inflammatory therapy (i.e., glucocorticoids and/or NSAIDs) for symptom control until the onset of action of DMARDs (e.g., ≥ 6 weeks).

Disease-modifying anti-rheumatic drugs (DMARDs)

- DMARD therapy reduces RA mortality and morbidity by up to 30%.
- If DMARD therapy induce disease control → reduce drug doses to levels that still maintain disease control.

Methotrexate (MTX)

- ⇒ first-line treatment in patients with moderate to high disease activity
- ⇒ All patients should be co-prescribed **folic acid** supplementation at a minimal dose of 5 mg once weekly to minimize adverse effects.
- ➡ Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis.
- ⇒ Other important side-effects include pneumonitis

Azathioprine (AZA)

Patients should have baseline thio-purine methyl-transferase (TPMT) status assessed

Sulfasalazine

Consider in patients with low disease activity if MTX is contraindicated, e.g., during pregnancy.

- ⇒ Adverse effects: diarrhea, agranulocytosis, cutaneous hypersensitivity reactions
- Hydroxychloroquine (HCQ)
 - ⇒ Consider in patients with low disease activity.
 - ⇒ Adverse effects: hyperpigmentation and retinopathy
 - ⇒ Patients should have baseline formal ophthalmic examination, ideally including objective retinal assessment for example using optical coherence tomography, within 1 year of commencing an antimalarial drug
- Leflunomide
 - ⇒ Consider if all other conventional DMARDs are contraindicated.
 - ⇒ **Mechanism of action:** reversibly inhibits dihydroorotate dehydrogenase → impaired pyrimidine synthesis → inhibition of T-cell proliferation
 - ⇒ Other indications: psoriatic arthritis

Monitoring rheumatoid arthritis

- Recommended DMARD Blood Monitoring Schedule when Starting or Adding a New DMARD (BSR guidelines February 2017)
 - ⇒ Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin
 - every 2 weeks until on stable dose for 6 weeks;
 - then once on stable dose, monthly for 3 months;
 - thereafter, at least every 12 weeks.
 - Contact rheumatology team urgently and consider interruption in treatment if any of the following develop:
 - white cell count $<3.5 \times 10^9$ /l;
 - mean cell volume >105 fL;
 - neutrophils <1.6 × 10⁹/l:
 - creatinine increase >30% over 12 months and/or calculated GFR <60 ml/min:
 - unexplained eosinophilia >0.5 × 10⁹/l;
 - ALT and/or AST >100 U/I:
 - platelet count <140 × 10⁹/l;
 - unexplained reduction in albumin <30 g/l
 - ⇒ In the setting of acute infection, most DMARDs (except hydroxychloroquine) should be discontinued until the infectious process has resolved.
- Measure CRP and key components of disease activity (using a composite score such as DAS28) regularly (monthly until treatment has controlled the disease) to inform decision-making about:
 - ⇒ increasing treatment to control disease
 - ⇒ cautiously decreasing treatment when disease is controlled.

The first-line treatment for newly diagnosed active RA → combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as soon as possible, ideally within 3 months of the onset of persistent symptoms.

TNF-inhibitor

- The current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- Examples of anti-TNF alpha agents:
 - ⇒ Etanercept: SC administration twice weekly
 - ⇒ Infliximab: IV administration
 - ⇒ Adalimumab: SC administration
- Adverse effects of TNF blockers include:
 - ⇒ reactivation of latent tuberculosis and demyelination.
 - ⇒ The risk of TB reactivation is most pronounced in the first 3 months of treatment.

- ⇒ BTS guidelines therefore recommend a clinical examination, and chest radiograph to check for TB.
- \Rightarrow In the UK, patients have a baseline CXR and assessment of risk of infection with Mycobacterium tuberculosis prior to starting treatment with anti-TNF α .
- Any patient with active TB,
 - ⇒ should receive standard chemotherapy.
 - They must complete two months full treatment before starting anti-TNF alpha treatment.
- Patients with past TB.
 - ⇒ who have received previous adequate therapy → can be started on anti-TNF alpha therapy but need to be monitored regularly.
 - ⇒ TB not previously adequately treated, → chemoprophylaxis should be given before commencing anti-TNF alpha treatment.
 - ⇒ What is the optimal TB screening test in patient with previous TB?
 - Interferon gamma release assay
 - ❖ The test is not altered by previous TB or previous BCG vaccination.
 - Positive testing indicates a need for anti-tuberculous treatment alongside golimumab, for example isoniazid.
 - Mantoux testing is less indicative of prior infection because it is likely to evoke a positive reaction in patients with previous TB or who have received BCG vaccination.
- Patients with a normal chest radiograph who have not started immunosuppressive threrapy → a tuberculin test is helpful.
- Patients with a normal chest radiograph + already on immunosuppressive treatment,
 - ⇒ the result of the tuberculin test is dampened and it is therefore not useful.
 - An individual risk assessment should be made: if the annual risk of TB is greater than that of drug-induced hepatitis then chemoprophylaxis should be given. If not, the patient should be monitored and investigated early if symptoms consistent with TB develop.
 - ⇒ Chemoprophylaxis is generally with isoniazid for 6 months.
- Patients who test positive with either of Quantiferon Gold test and Elispot tests should be treated with chemoprophylaxis (either isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time as being started on anti-TNF alpha treatment.
- TNF-inhibitors should be stopped 2-4 wks before any major operation.

Rituximab

- Action
 - ⇒ Anti-CD20 monoclonal antibody, results in B-cell depletion.
- Prescription
 - ⇒ Two doses of 1g intravenous infusions are given two weeks apart.
- Indications
 - ⇒ rheumatoid arthritis
 - Nice guidelines of RA → Rituximab in combination with methotrexate is recommended as an option for treatment of rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying antirheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.
 - ⇒ non-Hodgkin lymphoma (The primary clinical use)
 - ⇒ idiopathic thrombocytopenic purpura.
- Follow up
 - ⇒ Treatment with rituximab plus methotrexate should be continued only if:
 - There is an adequate response following initiation of therapy.
 - An adequate response is defined as an improvement in disease activity score

(DAS28) of 1.2 points or more.

 Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.

Side effects:

- ⇒ risk of reactivation of hepatitis B,
 - patients should be screened for previous exposure to hepatitis B prior to starting rituximab;
 - those with lone anti-hep B core antibodies should be treated with chemoprophylaxis (eg lamivudine) prior to rituximab.
- ⇒ Risk of Progressive multifocal leukoencephalopathy

Biologic DMARDs

- Indication:
 - ⇒ persistent moderate or severe disease activity after 3 months of conventional DMARD therapy
- Agents
 - ⇒ TNF-α inhibitors: e.g., adalimumab, infliximab, etanercept (see also "Contraindications to anti-TNF-α treatment")
 - Others: rituximab (anti-CD20), anakinra (IL-1 receptor antagonist, particularly for Still disease), tocilizumab (IL-6 receptor antagonist)
- Adverse effects include:
 - ⇒ Infections
 - ⇒ TB reactivation
 - ⇒ Hepatitis B reactivation

Rheumatoid arthritis: Management in pregnancy

Key points

- patients with early or poorly controlled RA should be advised to defer conception until their disease is more stable
- RA symptoms tend to improve in pregnancy but only resolve in a small minority. Patients tend to have a flare following delivery
- patients should be referred to an obstetric anaesthetist due to the risk of atlanto-axial subluxation

Effect of pregnancy on rheumatoid arthritis

- 50 to 70% of women with rheumatoid arthritis (RA) improve during pregnancy
- 50% of patients eventually **flare during the postpartum period**, usually within the first three months.
- The risk of developing RA increased in the first three months postpartum

Effect of RH on pregnancy

- · RA does not increase fetal losses.
- Higher rate of intrauterine growth restriction, pregnancy-induced hypertension, and cesarean delivery

Medications in pregnancy

- Contraindicated in pregnancy
 - Methotrexate (teratogenic): needs to be stopped at least 3 months before conception
 - ⇒ leflunomide

Preferred medications (if required)

- ⇒ NSAIDs: may be used until 32 weeks but after this time should be withdrawn due to the risk of early close of the ductus arteriosus. considered category B earlier in the pregnancy
- ⇒ Sulfasalazine
- ⇒ hydroxychloroguine
- Medications relatively safe to use (require individualized approach)
 - ⇒ TNFα inhibitors
 - ⇒ Azathioprine

Medications in breast feeding

- Breast feeding is not recommended with azathioprine.
- Prednisolone and hydroxychloroquine may be taken whilst breast-feeding.
- Azathioprine, cyclophosphamide, methotrexate and cyclosporine are contraindicated in breast-feeding mothers.

RA during pregnancy → continue current dose of azathioprine and add folic acid

Felty's syndrome

Definition

- a severe subtype of RA characterized by neutropenia and splenomegaly
- It is considered an extra-articular manifestation of rheumatoid arthritis.

Epidemiology

• occur in less than 1% of patients with rheumatoid arthritis.

Risk factors

- usually occurs in patients with long-standing seropositive RA.
- HLA subtype (HLA DRW4) is found in 95% of patients with Felty syndrome compared with 70% of people with rheumatoid arthritis alone.

Feature

- Triad of arthritis, splenomegaly, and neutropenia (absolute neutrophil count <2000/microL)
- Neutropenia increases risk of recurrent bacterial infections.
- ANA is positive in more than 90% of patients

Treatment

- Most appropriate initially → Pulsed corticosteroid therapy
- $\bullet \quad \text{First line} \to \text{Disease-modifying anti-rheumatic drugs (DMARDs): methotrexate} \\$
- Second line (If no response to methotrexate) → rituximab (RTX)
- granulocyte colony-stimulating factor (G-CSF, filgrastim) to stimulate production of granulocytes.
- Splenectomy: usually reserved for patients with severe neutropenia and recurrent infections who fail to respond to medical intervention.

Felty's syndrome →Triad of arthritis, splenomegaly, and neutropenia

Seronegative spondyloarthropathies

Common features

- associated with HLA-B27
- rheumatoid factor negative hence 'seronegative'
- · peripheral arthritis, usually asymmetrical
- sacroiliitis
- · enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- extra-articular manifestations: uveitis, pulmonary fibrosis (upper zone), amyloidosis, aortic regurgitation

Spondyloarthropathies

- · ankylosing spondylitis
- · psoriatic arthritis
- Reiter's syndrome (including reactive arthritis)
- enteropathic arthritis (associated with IBD)

Adhesive capsulitis

Overview

 Adhesive capsulitis (frozen shoulder) is a common cause of shoulder pain. aetiology of frozen shoulder is not fully understood.

Risk factors

- Adhesive capsulitis is a recognised musculoskeletal complication of diabetes (40% of diabetic patients developing this problem at some stage.)
- occurs more commonly in women after age 50

Features

- Severe restriction of both active and passive range of movement of the glenohumeral joint in all planes (especially external rotation)
- · Dull shoulder pain

Diagnosis

- · Radiographs of the shoulder show osteopenia.
- The diagnosis is confirmed by arthrography.

Management

- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral and intra-articular corticosteroids

Prognosis

· Self-limiting condition that usually resolves within 18 to 24 months

Ankle injury: Ottawa rules

- The Ottawa Rules for ankle x-rays have a sensitivity approaching 100%
- An ankle x-ray is required only if there is any pain in the malleolar zone and any one of the following findings:
 - 1. bony tenderness at the lateral malleolar zone (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)

- 2. **bony tenderness at the medial malleolar zone** (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
- 3. inability to walk four weight bearing steps immediately after the injury and in the emergency department
- There are also Ottawa rules available for both foot and knee injuries

Ankylosing spondylitis

Ankylosing spondylitis features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- · Achilles tendonitis
- AV node block
- Amyloidosis

Ankylosing spondylitis - x-ray findings: subchondral erosions, sclerosis and squaring of lumbar vertebrae

Definition

• Seronegative spondyloarthropathy that involves chronic inflammatory disease of the spine and sacroiliac joints.

Pathophysiology

- Autoimmune disorder, 90-95% of patients are HLA-B27 positive
- It has a polygenic inheritance.

Epidemiology

- Typically presents in males (sex ratio 3:1)
- Age: 20 40 years

Features

Typically a young man who presents with lower back pain and stiffness of insidious onset

- Articular manifestations
 - ⇒ Spinal joint pain
 - Features of inflammatory back pain (most common presenting symptom)
 - Morning stiffness > 30 minutes that improves with activity
 - usually worse in the morning and improves with exercise
 - Pain is independent of positioning
 - Tenderness over the sacroiliac joints (positive Mennell's sign)
 - Reduced spinal mobility, reduced lateral flexion
 - Reduced forward flexion → positive Schober's test (restriction in the lumbar flexion when patient asked to touch his toes while keeping the knees straight.)
 - Accentuated thoracic kyphosis
 - Loss of lumbar lordosis

⇒ Extraspinal joint pain

- Inflammatory enthesitis (the point where a tendon attaches to a bone)
- Dactylitis (an inflammation of the fingers and/or toes)
- Arthritis outside the spine, peripheral arthritis (25%, more common in female)

Extraarticular manifestations

⇒ Anterior uveitis

- The most common extra-articular manifestations (in around 40% of patients)
- Usually acute, unilateral anterior uveitis
- more common in B27 positive than B27 negative patients.
- ⇒ Fatigue

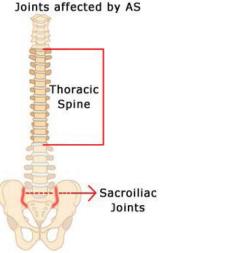
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- ⇒ Restrictive pulmonary disease → **thest expansion on deep breathing** due to decreased mobility of the thoracic spine and costovertebral joints
- ⇒ GIT symptoms of inflammatory bowel disease (diarrhea with blood) (5%)
- Aortic root inflammation and subsequent aortic valve insufficiency, atrioventricular blocks
- ⇒ IgA-nephropathy

Ankylosing spondylitis: Diagnostic criteria

- Cower back pain for > 3 months in patients < 45 years of age and one of the following:</p>
 - Sacroiliitis confirmed on x-ray or MRI and ≥ 1 typical clinical or laboratory finding
 - A positive HLA-B27 test and ≥ 2 typical clinical or laboratory findings





Investigations

the best option to confirm a diagnosis of ankylosing spondylitis → Sacroiliac joints x ray

- Inflammatory markers (ESR, CRP) are typically **raised** although normal levels do not exclude ankylosing spondylitis.
- HLA-B27 is of little use in making the diagnosis because it is positive in 90% of patients with ankylosing spondylitis and 10% of normal patients. The likelihood of a positive test depends on the racial and ethnic background of the patient
 - ⇒ The commonest subtype HLA associations are:
 - HLA B*2705 (Caucasians)
 - **B*2704** (Chinese, Japanese)
 - B*2702 (Mediterranean).
 - The B*2706 subtype is weakly associated and commonly found in normal south east Asian individuals.
- Autoantibodies (e.g., rheumatoid factor, antinuclear antibodies) are negative
- Radiographs
 - Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis.
 - ⇒ Radiographs may be normal early in disease, later changes include:
 - sacroilitis: subchondral erosions, sclerosis
 - squaring of lumbar vertebrae
 - 'bamboo spine' (vertebral fusion) (late & uncommon)
 - Syndesmophytes: due to ossification of outer fibers of annulus fibrosus (the tramline appearance is due to syndesmophyte growth between the margins of the vertebrae)
 - Syndesmophytes grow vertically, as opposed to spondylophytes, which grow horizontally
 - Chest x-ray: apical fibrosis

Syndesmophytes grow vertically, as opposed to osteophytes, which grow horizontally

Syndesmophytes vs. osteophytes			
	Syndesmophytes	Osteophytes	
Definition	 Ossification or calcification of the annulus fibrosus or a spinal ligament 	Lipping of vertebral bodies	
Radiographic features	 Symmetrical, vertical growth, directly from vertebral body to vertebral body Full manifestation: "bamboo spine" 	Horizontal growth	
Etiology	Inflammatory spine disease (e.g., AS)	Degenerative spine disease (e.g., diffuse idiopathic skeletal hyperostosis)	



40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners.

Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

- MRI: More sensitive than x-ray (Best method for early detection)
 - ⇒ Shows:
 - Bone marrow edema (The earliest change visible on MRI)
 - Squaring of the vertebrae,
 - Erosion of apophyseal joint
 - Obliteration of sacroiliac joint
 - Spirometry may show a restrictive defect due to a combination of <u>pulmonary fibrosis</u>, kyphosis and ankylosis of the costovertebral joints.

Diagnosis → New York criteria

- Current British Society for Rheumatology recommendations state that the modified New York criteria should be used to diagnose ankylosing spondylitis:
 - ⇒ Clinical criteria:
 - Low back pain, present for more than three months, improved by exercise but not relieved by rest
 - Limitation of lumbar spine motion in both the sagittal and frontal planes
 - Limitation of chest expansion relative to normal values for age and sex.
 - ⇒ Radiological criteria:
 - Sacroilitis on x ray.
 - **⇒** Diagnosis:
 - Definite AS if the radiological criterion is present plus at least one clinical criterion

 Probable AS if three clinical criteria are present alone or if the radiological criterion is present but no clinical criteria are present.

Management

- Non-pharmacological: encourage regular exercise such as swimming, physiotherapy
 - Pharmacological
 - ⇒ First-line pharmacotherapy in most patients: NSAIDs
 - ⇒ Second-line : TNF-α inhibitors (e.g., etanercept, adalimumab)

Avascular necrosis (AVN)

Definition

• death of bone tissue due to interruption of blood supply; most commonly affects the epiphysis of long bones such as the femur.

Causes

- · long-term steroid use
- sickle cell disease, Gaucher disease
- Cellular toxicity (e.g., **chemotherapy**, radiotherapy, alcohol excess)
- trauma

Features

- · initially asymptomatic
- pain in the affected joint

Investigation

- plain x-ray findings may be normal initially
- MRI is the investigation of choice. It is more sensitive than radionuclide bone scanning

Treatment

• Joint replacement (e.g., hip, shoulder, knee)

Behcet's syndrome

Oral ulcers + genital ulcers + anterior uveitis = Behcet's

Definition

- Behcet's syndrome is a systemic vasculitis that is characterized by autoimmune mediated inflammation of the arteries and veins.
- affects small and large vessels (venous and arterial).

Pathophysiology

- Autoimmune (involves mainly the T <u>helper</u> cells) and infectious triggers (e.g., precipitating HSV or parvovirus infection)
- Strong **HLA-B51** association
 - ⇒ HLA B5 is associated with ocular disease:
 - ⇒ HLA B12 is associated with recurrent oral ulcers.

Epidemiology

- More common in the eastern Mediterranean (e.g. Turkey)
- More common and more severe in men
- Tends to affect young adults (e.g. 20 40 years old)
- Around 30% of patients have a positive family history

Features

- Recurrent painful oral aphthous ulcers: (95–100%): Usually last about 1–4 weeks
- · Recurrent genital ulcerations
- Ocular disease (50–80%) → Uveitis

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- Skin lesions (35–85%)
- Erythema nodosum
- Vasculopathy: Superficial thrombophlebitis, DVT
- Seronegative arthritis: Usually <u>asymmetric</u> arthritis.
- Neurological involvement (e.g. aseptic meningitis)
- GI: abdominal pain, diarrhoea, colitis
- Pathergy (development of pustules at venepuncture sites).
- Fever

Behcet's syndrome: The classic triad of symptoms are:

- 1. Oral ulcers
- 2. Genital ulcers
- 3. Anterior uveitis (iritis)

Behcet's syndrome → PATHERGY

Positive pathergy test, Aphthous mouth ulcers, Thrombosis (arterial and venous), Hemoptysis (pulmonary artery aneurysm), Eye lesions (uveitis, retinal vasculitis), Recurrent Genital ulcers, Young at presentation (3rd decade)

Diagnosis

- No definitive test. Diagnosis based on clinical findings
- Positive pathergy test is suggestive (puncture site following needle prick becomes inflamed with small pustule forming) → specific to Behcet's disease. It involves intradermal injection of skin with a 20-gauge needle under sterile conditions. It is considered positive if an erythematous sterile papule develops within 48 hours.
- Autoantibodies (e.g., ANA, ANCA, rheumatoid factor) are usually absent.
- Diagnostic criteria (International Study Group criteria)
 - ⇒ Recurrent oral ulceration at least three times within a 12-month period AND ≥ 2 of the following
 - Recurrent genital ulceration
 - Eye lesions
 - Skin lesions
 - Positive pathergy test

Treatment

- · Oral ulcers and/or genital ulcers: topical corticosteroids, topical lidocaine for pain relief
- . Arthritis or Erythema nodosum: Colchicine is the first line treatment.
- Ocular disease, CNS disease, and/or vasculopathy
 - ⇒ Systemic corticosteroids
 - Immunosuppressant therapy (e.g., azathioprine, infliximab, cyclosporine A, cyclophosphamide, IFN-α, methotrexate)

Chronic fatigue syndrome

Definition

- Diagnosed after at least 4 months of disabling fatigue affecting mental and physical function more than 50% of the time in the absence of other disease which may explain symptoms.
- also known as myalgic encephalomyelitis

Epidemiology

- More common in **females** and young to middle-aged adults.
- Past psychiatric history has NOT been shown to be a risk factor

Fatigue is the central feature, other recognised features include

- Sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleepwake cycle
- Muscle and/or joint pains
- Headaches
- · Painful lymph nodes without enlargement
- Recurrent sore throat
- Cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- Physical or mental exertion makes symptoms worse
- General malaise or 'flu-like' symptoms
- Dizziness
- Nausea
- Palpitations

To confirm a diagnosis of fatigue the following main features need to be present:

- Must be new in onset, persistent or recurrent and unexplained by other conditions.
- Should be characterised by post-exertional malaise.
- Should result in a substantial reduction in activity level.

Red flag symptoms which suggest another diagnosis include:

- · Significant weight loss
- Inflammatory arthropathy or connective tissue disease
- · Localising or focal neurological signs.

Investigation

 NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin* (*children and young people only), coeliac screening and also urinalysis

Management

- · Treatment of choice: graded exercise therapy
 - ⇒ a formal supervised program,
 - ⇒ not advice to go to the gym
 - ⇒ 'pacing' organising activities to avoid tiring
- · Cognitive behaviour therapy very effective,
- Low-dose amitriptyline may be useful for poor sleep
- Referral to a pain management clinic if pain is a predominant feature

Prognosis

- The short-term prognosis for recovery of function is generally poor. The long-term prognosis appears to be better
- Better prognosis in children

Chronic fatigue syndrome (also known as myalgic encephalomyelitis) \rightarrow unexplained, persistent, and relapsing fatigue.

Compartment syndrome

Pain with passive stretching of the muscles, is the earliest clinical indicator of compartment syndrome.

Pathophysiology

External or internal forces as initiating event → increased compartment pressure →
obstruction of venous outflow and collapse of arterioles → decreased tissue perfusion →
lower oxygen supply to muscles → irreversible tissue damage (necrosis) to muscles and
nerves after 4–6 hours of ischemia

Features

- Early presentation
 - ⇒ Pain
 - Often out of proportion to the extent of injury
 - Worse with passive stretching or extension of muscles
 - Very tight, wood-like muscles that are extremely tender to touch
 - ⇒ Sensory deficit in the distribution of the peripheral nerve(s) passing through that compartment
 - Paresthesia (e.g., pins and needles)
 - Decreased 2-point discrimination is the most consistent early finding
 - in acute anterior lower leg compartment syndrome, the first sign to develop may be numbness between the first 2 toes (superficial peroneal nerve).
 - ⇒ Soft tissue swelling
- Late presentation
 - ⇒ Muscle weakness to paralysis
 - ⇒ Cold peripheries
 - ⇒ Pallor
 - ⇒ Absent (or weak) distal pulses

Complications

- · Muscle and soft tissue necrosis
- Nerve lesions (esp. the tibial nerve and peroneal nerve) with sensory and motor deficits or paralysis
- Rhabdomyolysis with potential Crush syndrome

Investigations

- A Creatine phosphokinase (CPK) concentration of 1000-5000 U/mL or greater or the presence of myoglobinuria can suggest compartment syndrome.
- Compartment pressure measurement (initial and confirmatory test)

Risk factors

- Trauma
- Anticoagulation therapy and bleeding disorders (eg, hemophilia)
- Vigorous exertion (has been found in soldiers and athletes without any trauma).

Treatment

- Surgical → Urgent decompression is required to prevent severe ischaemia.
 - ⇒ Fasciotomy (tissue and fascia incisions): relieves the pressure, thus restoring perfusion
 - ⇒ Escharotomy: in the case of circumferential compression by a burn eschar

Acute compartment syndrome is a surgical emergency and requires an early fasciotomy. Elevated positioning may worsen ischemia by reducing blood flow.

Complex regional pain syndrome (CRPS)

Epidemiology

• Three times more frequent in females than males

Pathophysiology

 Unknown. Proposed mechanisms include classic inflammation, neurogenic inflammation, and maladaptive changes in pain perception at the level of the central nervous system.

Precipitating factors

- injury and surgery (fractures and soft tissue injuries.): most common
- CRPS seldom occurs in the absence of an identifiable trigger.

Features

- Severe pain out of proportion to the original injury
- Sensory changes, motor impairments, autonomic symptoms, and trophic changes in the affected limb.
 - ⇒ **Allodynia** (perception of pain from a nonpainful stimulus)
 - ⇒ **Hyperalgesia** (an exaggerated sense of pain)

A repeat X-ray is the most appropriate next investigation looking for patchy osteoporosis in patient developed clinical features consistent with complex regional pain syndrome type 1 (CRPS1)

Cryoglobulinaemia

consumption of C4 + strongly positive rheumatoid factor → cryoglobulinaemia.

Overview

- Cryoglobulins are abnormal immunoglobulins which precipitate when cooled below 37°C (maximum precipitate formation takes place at +4°C) and redissolve in plasma when warmed back to 37°C (reversible precipitation at low temperatures)
- The precipitated clump can block blood vessels and cause toes and fingers to become gangrenous.
- Cryoglobulins usually consist of IgM directed against the Fc region of IgG.
- Common causes: hepatitis C, multiple myeloma, SLE, rheumatoid arthritis, Idiopathic (one third of cases)

Pathophysiology

- Immune deposition on the wall of small vessels result in generalized vasculitis, which
 presents with a reticulated skin pattern of micro-thrombosis and areas of gangrene.
- cryoglobulins → form an immune complexes → activate the complement system, resulting in ⊥complement levels (Hypocomplementemia)

Three types

- Type I (25%):
 - ⇒ monoclonal (lgG or lgM)
 - ⇒ associated with haematological diseases such as myeloma and Waldenstrom's.
- Type II (25%):
 - ⇒ Mixed monoclonal and polyclonal: usually with RF
 - ⇒ Composed of a monoclonal IgM rheumatoid factor plus polyclonal IgG
 - ⇒ Associations: hepatitis C, RA, Sjogren's, lymphoma

- most importantly, hepatitis C infection which should always be excluded.
 - If serological testing is negative, then the cryoprecipitate should be checked for HCV RNA by PCR.
 - Membranoproliferative glomerulonephritis (also known as mesangiocapillary glomerulonephritis) is the characteristic histological finding on biopsy where there is renal involvement.
 - For hepatitis C associated mixed cryoglobulinaemia, interferon alpha is the treatment of choice, although rapidly progressive disease may require immunosuppressive therapy.
- Type III (50%):
 - ⇒ polyclonal: usually with RF
 - ⇒ composed of a polyclonal IgM rheumatoid factor plus polyclonal IgG.
 - ⇒ associations: RA, Sjogren's

Mixed cryoglobulinemia

- Types II and III cryoglobulinemia
- both type II and III cryoglobulinaemia have rheumatoid factor reactivity
- represent 80% of all cryoglobulins.
- contain rheumatoid factors (RFs) which are usually IgM
- closely associated with hepatitis C virus (HCV)

Symptoms (if present in high concentrations)

Meltzer's triad (seen in cryoglobulinaemia (types II/III)→ palpable purpura, arthralgia and myalgia

- Raynaud's only seen in type I
- Cutaneous: vascular purpura, distal ulceration
 - ⇒ skin is most commonly involved organ (over 90%), with purpura, leg ulcers and acrocyanosis.
- Arthralgia (seen in 70%).
- Renal involvement (diffuse glomerulonephritis)
 - ⇒ Glomerular disease is common in types 2 and 3 (mixed types) and occurs in around 50–55% of cases.
- Axonal <u>peripheral neuropathy</u>
 - ⇒ cryoglobulins → small-vessel vasculitis → axonal peripheral neuropathy
 - ⇒ may be sensorimotor, or purely sensory.
 - ⇒ Neurological involvement (polyneuropathy) is seen in 40% of patients.
- Pulmonary embolism, arterial and venous thrombosis are common.
- The gastrointestinal tract is affected in 30%.

A <u>vasculitic rash</u> and <u>neuropathy</u> in a patient with <u>hepatitis C</u> is suggestive of cryoglobulinaemia.

Tests

- **low complement (esp. C4):** occurs in about 90% of patients with mixed cryoglobulinaemia (Type II) as a result of classic pathway activation.
- Since they precipitate at low temperatures, cryoglobulins should always be transported to
 the lab at 37°C. Failure to do this will result in a false negative result as the cryos will
 precipitate and be removed with the clot.
- High ESR

Treatment

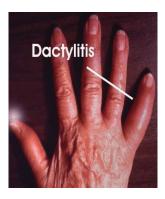
- immunosuppression (high dose steroids and cyclophosphamide).
- Plasmapheresis

Hypocomplementemia is seen in many conditions, including:

- Lupus,
- Mixed cryoglobulinemia,
- Membranoproliferative glomerulonephritis, and
- Hereditary angioedema.

Dactylitis

- Dactylitis describes the inflammation of a digit (finger or toe).
- . A 'sausage-shaped' digit is a classical description of dactylitis
- Causes include:
 - ⇒ spondyloarthritis: e.g. Psoriatic and reactive arthritis
 - ⇒ sickle-cell disease
 - ⇒ other rare causes include tuberculosis, sarcoidosis and syphilis



De Quervain's tenosynovitis

- De Quervain's tenosynovitis is a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed.
- It is a common pathology which consists of a stenosing tenosynovitis of the first dorsal compartment of the wrist.
- It typically affects females aged 30 50 years old

Causes

- commonly caused by occupational or avocational repetitive movement of the thumb
- also associated with RA, psoriatic arthritis, direct trauma, pregnancy, and the post-partum period.

Features

- · pain on the radial side of the wrist
- tenderness over the radial styloid process
- abduction of the thumb against resistance is painful
- · Finkelstein's test:
 - ⇒ Used to confirm the diagnosis
 - ⇒ the patient is asked to bring the thumb across the palm and clasp the fingers around it. The examiner then pulls it in the ulnar direction, which elicits a sharp pain.

Management

- analgesia
- · steroid injection
- · immobilisation with a thumb splint (spica) may be effective
- · surgical treatment is sometimes required

Scaphoid fractures

- are relatively common,
- typically occurring following a fall onto outstretched hand.
- The proximal portion lacks its own blood supply, so <u>avascular necrosis</u> can occur if a fracture leaves it isolated from the remainder of the scaphoid.
- produces <u>pain and tenderness of the radial side of the wrist</u>, classically in the anatomical snuffbox, exacerbated by wrist movement.
- · Preiser's disease is avascular necrosis of scaphoid

Gout

The vast majority of gout is due to decreased renal excretion of uric

Gout: start allopurinol if >= 2 attacks in 12 month period

Definition

 An inflammatory crystal arthropathy that is caused by the precipitation and deposition of uric acid crystals in synovial fluid and tissues. It is typically associated with hyperuricemia, but can also occur if uric acid levels are normal.

Epidemiology

- Gout is the most prevalent form of inflammatory arthropathy.
- Sex: ♂ > ♀ (3:1)
- Age of onset: 2 peaks of incidence (at 30–39 years and at 60 years of age)

Pathophysiology |

- Uric acid is an end-product of purine metabolism that is excreted by the kidneys, predisposes to gout
- Chronic hyperuricaemia (uric acid > 0.45 mmol/l) → intraarticular uric crystal precipitation (deposition of monosodium urate monohydrate in the synovium) → release of inflammatory mediators and enzymes → aggregations of urate crystals and giant cells (tophi) → local joint inflammation (microcrystal synovitis), arthritis and deformities

Causes

- Decreased uric acid excretion via the kidney → most common cause (90%)
 - Medications (e.g., pyrazinamide, aspirin, loop diuretics, thiazides, niacin, cytotoxic agents)
 - Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels
 - If diuretics are being used to treat hypertension an alternative antihypertensive should be considered, but they should not be stopped in the presence of heart failure.
 - ⇒ Chronic renal insufficiency
 - ⇒ Ketoacidosis; due to, e.g., starvation → ↑lactic acid → impairs the kidneys' ability to excrete uric acid →↑ risk of gout)

- ⇒ Postmenopause
- Increased uric acid production (10%)
 - ⇒ High cell turnover, e.g.:
 - Tumor lysis syndrome
 - Hemolytic anemia
 - Psoriasis
 - Myeloproliferative neoplasms
 - ⇒ Enzyme defects, e.g.:
 - Lesch-Nyhan syndrome
 - Phosphoribosyl pyrophosphate synthetase overactivity
 - von Gierke disease
 - ⇒ Diet rich in protein and especially purine (e.g., red meat, seafood)
 - ⇔ Obesity
 - ⇒ Hypercholesterolemia, hypertriglyceridemia
 - ⇒ Hypertension
- Combined decreased excretion and overproduction: high alcohol consumption
 - ⇒ Organic acids from alcohol metabolism compete with uric acid to be excreted by the
- Can be idiopathic (primary hyperuricemia): Primary hyperuricemia can be aggravated by poor dietary habits.

Drugs associated with gout: aspirin, thiazides, niacin, pyrazinamide, loop diuretics.

Lesch-Nyhan syndrome

- hypoxanthine-quanine phosphoribosyl transferase (HGPRTase) deficiency
- x-linked recessive therefore only seen in boys
- features: gout, renal failure, neurological deficits, learning difficulties, aggressiveness, self-mutilation (for example, biting of finger tips and/or lips).

What is the most common cause of acute gout in association with G-6PD deficiency?

- Increased production of pentose sugars
 - ⇒ Glucose-6-phosphate dehydrogenase (G6PD) → converts (G6P) to glucose.
 - \Rightarrow (G6PD) Deficiency \rightarrow accumulation of G6P \rightarrow enters the hexose monophosphate shunt $\rightarrow \uparrow$ production of pentose sugars. (These act as a substrate for phosphoribosyl pyrophosphate (PRPP) synthetase) $\rightarrow \uparrow$ production of purines → uric acid.
 - \Rightarrow Hypoglycaemia in G6PD deficiency $\rightarrow \uparrow$ catecholamine levels $\rightarrow \uparrow$ glycogenolysis in muscles $\rightarrow \uparrow$ lactic acidosis $\rightarrow \downarrow$ urate excretion (competes with uric acid for excretion)

Features

- Acute gouty arthritis
 - ⇒ Acute severe pain with overlying erythema, decreased range of motion, swelling, warmth
 - Symptoms are more likely to occur at night, typically waking the patient.
 - peak after 12-24 hours
 - ⇒ Desquamation of the skin
 - ⇒ Location: Usually monoarthritis during first attacks
 - Asymmetrical distribution is common if more than one joint is affected
 - Metatarsophalangeal joint (MTP joint) inflammation of the big toe (the most common site)
 - Knee, finger, ankle; wrist

Chronic gouty arthritis

- ⇒ Progressive joint destruction
- Tophi formation: Multiple painless hard nodules with possible joint deformities, appear yellow or white. Ulceration and discharge (chalky white substance) may occur
 - Bone tophi: urate crystal deposition in bones (e.g., elbows, knees, extensor surfaces of forearms)
 - Soft tissue tophi: urate crystal deposition in the pinna of the external ear, subcutis, tendon sheaths (e.g., at the Achilles tendon), or synovial bursae (e.g., olecranon bursa)
- ⇒ Uric acid nephrolithiasis and uric acid nephropathy

Investigations

- WBC and ESR are typically elevated
- Serum urate
 - often elevated (hyperuricemia); may also be normal or low; (normal urate concentration does not rule out a diagnosis of gout).
 - ⇒ Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout
- X-ray: the <u>bony erosions are typically punched out</u> with sclerotic margins and overhanging edges, sometimes termed rat bite erosions.
- **Joint aspiration** → **Presence of long needle-shaped Crystals** (uric acid crystal)
 - ⇒ gold standard for diagnosing gout
 - ⇒ Findings
 - Needle-shaped monosodium urate crystals that are negatively birefringent
 - Synovial fluid cell count: WBC > 2000/µL with > 50% neutrophils



There is well defined **punched-out** juxtaarticular erosions related to both sides of the first metatarsal bone. This is a classical site for gout.

Management

- · Lifestyle modifications may help reduce the risk of flares.
 - ⇒ Limit alcohol consumption
 - ⇒ Limit intake of purines (e.g., red meat and shellfish)
 - ⇒ Weight loss if patient is overweight
- Acute gout flare → First-line agents: NSAIDs, colchicine or glucocorticoids
 - ⇒ **NSAIDs** (Naproxen: indomethacin, ibuprofen)
 - Add a proton pump inhibitor to reduce the risk of gastrointestinal ulcers.
 - Should be avoided in elderly patients taking warfarin due to the risk of a life-threatening gastrointestinal haemorrhage.
 - Contraindicated in renal impairment (use colchicine in mild to moderate CKD and prednisolone in severe CKD)
 - Relatively contraindicated in congestive cardiac failure

- Mechanism of action: binds and stabilizes tubulin subunits → inhibits microtubule polymerization → inhibits phagocytosis of urate crystals, neutrophil activation, migration, and degranulation
- Useful in patients taking warfarin as combined NSAID is harmful to GIT.
- Can be used in mild and moderate CKD (not severe CKD). The BNF advises
 to reduce the dose by up to 50% if creatinine clearance is less than 50 ml/min
 and to avoid if creatinine clearance is less than 10 ml/min.
- May be increased up to a dose of 3mg, divided in 600mcg portions to cope with the acute attack.
- The most appropriate management for patient on colchicine 600mcg daily presented with acute gout and mild renal impairment →Increase his colchicine to cope with the exacerbation
- Side effects
 - Diarrhea (the main side-effect)
 - Myopathy, rhabdomyolysis
 - Polyneuropathy
 - CNS symptoms (e.g., fatigue, headache)
 - Myelosuppression
 - Cardiac toxicity, arrhythmias
- Contraindications: Severe CKD
- Drug interactions
 - Statins: Consider reducing dose of pravastatin, atorvastatin, or simvastatin when prescribed concomitantly.
 - Potent cytochrome P450 3A4 substrates or inhibitors
 - $\hfill \square$ Reduce colchicine dose when prescribed concomitantly.
 - Avoid in patients with CKD or hepatic impairment.
- ⇒ **Glucocorticoids** (prednisolone, methylprednisolone, or intraarticular administration)
 - Glucocorticoids are preferable if there are contraindications (e.g., CKD), intolerance, or inadequate response to NSAIDs or colchicine.
 - A recent trials found that oral prednisolone (30 mg/day for 5 days) had analgesic effectiveness equivalent to that of indomethacin and naproxen.
 - Avoided in diabetics because it would adversely affect diabetic control.
 - intraarticular steroid are preferred for NPO patients

⇒ IL-1 blockers

- European Medicines Agency approved anti-IL-1β monoclonal antibody canakinumab (150 mg subcutaneously, one dose) for patients with contraindication to colchicine, NSAIDs and steroids
- Current infection is a contraindication to the use of IL-1 blockers.
- ⇒ Rest the affected joints

Low-dose aspirin can decrease uric acid excretion and trigger recurrent gout flares but it should not be stopped in patients taking it for specific indications (e.g., coronary artery disease, cerebrovascular disease), regardless of the severity of gout.

Monitor for myotoxicity when prescribing colchicine with statins. Reduce dose of pravastatin, atorvastatin, and simvastatin when prescribed concomitantly.

- Chronic gout → Urate-lowering therapy (ULT)
 - ⇒ **First-line**: xanthine-oxidase inhibitors (allopurinol)
 - ⇒ **Second-line:** uricosurics (probenecid)
 - ⇒ **Third-line:** recombinant uricase (pegloticase)
 - ⇒ Absolute indications
 - Damage due to chronic gout seen on imaging
 - Tophi development
 - Frequent gout attacks (≥ 2 per year)
 - ⇒ Relative indications
 - < 2 gout attacks per year</p>
 - First episode of acute gout flare in patients with any of the following risk factors:
 - CKD ≥ stage 3
 - Serum uric acid > 9 mg/dL
 - History of urolithiasis
 - **⇒** Contraindications to all ULT agents
 - Acute gout flare (in the absence of the above-mentioned risk factors). If the patient is already taking allopurinol it should be continued.
 - Asymptomatic hyperuricemia
 - ⇒ **Timing of initiating ULT:** at least one week after initiating anti-inflammatory prophylaxis as ULT may trigger, prolong, or worsen an acute gout flare.
 - ⇒ Target of serum uric acid: < 6 mg/dL (360 µmol/L).
 </p>

Urate-lowering therapy (ULT)

- Xanthine oxidase inhibitors (XOIs): Allopurinol and Febuxostat (the preferred firstline agent)
 - ⇒ Action:
 - Allopurinol is a competitive inhibitor.
 - Febuxostat is a non-purine, selective inhibitor of xanthine oxidase that is metabolized in the liver. Recommended by NICE guidance as secondchoice to prevent gout when allopurinol has not been tolerated or is contraindicated.
 - **⇒** Contraindications
 - Allopurinol: Presence of the HLA-B*5801 allele
 - Febuxostat: History of cardiovascular disease
 - ⇒ Side effects
 - Allopurinol: Stevens-Johnson syndrome/toxic epidermal necrolysis
 - Febuxostat: Nausea, diarrhea, transaminitis

□ Interactions

- Purine analogs (e.g., azathioprine, 6-mercaptopurine) combined with XOIs can cause bone marrow toxicity
- Probenecid and thiazides decrease the efficacy of allopurinol
- Allopurinol increase INR by inhibiting the metabolism of warfarin.
- Uricosurics: Probenecid (the second line)
 - ⇒ Action: Inhibition of uric acid reabsorption along renal proximal convoluted tubules → increased renal elimination
 - ⇒ Contraindications
 - Nephrolithiasis
 - Moderate to severe CKD
 - ⇒ **Side effects:** Urolithiasis (uric acid stones)
 - ⇒ Interactions: Inhibits penicillin secretion in the proximal convoluted tubule
- Recombinant uricase: Pegloticase (the third line)
 - ⇒ Action: breakdown of uric acid to allantoin (allantoin is water-soluble and therefore can be renally excreted)
 - ⇒ **Contraindications:** G6PD deficiency, Congestive heart failure

The combination of allopurinol and azathioprine leads to increased bone marrow toxicity

Rasburicase

- · recombinant urate oxidase
- may be given during the acute attack of gout, to allow allopurinol therapy to be commenced without the initial worsening of symptoms.
- But it is not currently licensed for the treatment of acute gout associated with other conditions.
- The best choice for warfarinsed patient

Acute gout pain with congestive cardiac failure and renal impairment, developed severe diarrhoea with colchicine. The treatment of choice → Prednisolone

Most patients with hyperuricaemia never develop gout or stones. Treatment of these patients is not recommended.

Allopurinol

- Allopurinol therefore
- Inhibit xanthine oxidase
- Reduces both purine breakdown and synthesis.
- Can be used even in moderate-severe renal failure with dose reduction
- NSAID or colchicine cover should be used when starting allopurinol

Allopurinol, Azathioprine interaction

- Azathioprine metabolised to active compound 6-mercaptopurine
- xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- Allopurinol can therefore lead to high levels of 6-mercaptopurine
- A much-reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided
- Allopurinol Increases toxicity and effects of azathioprine and 6-mercaptopurine. So reduce dose of azathioprine and 6-mercaptopurine to one quarter of usual dose.

Antihypertensive drugs and gout

- Antihypertensive either increase serum uric acid levels (e.g., diuretics, β-blockers) or decrease serum uric acid levels (e.g., calcium-channel blockers, losartan).
- Losartan has a specific uricosuric action (\(\frac{1}{2}\)excretion of uric acid in the urine, thus reducing
 the serum uric acid) and may be particularly suitable for the many patients who have
 coexistant hypertension

Prognosis

- Gout appears to be an independent risk factor for cardiovascular mortality and morbidity
- Hyperuricaemia may be associated with both hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Hip pain in adults

The table below provides a brief summary of the potential causes of hip pain in adults

Condition	Features	
Osteoarthritis	Pain exacerbated by exercise and relieved by rest Reduction in internal rotation is often the first sign Age, obesity and previous joint problems are risk factors	
Inflammatory arthritis	Pain in the morning Systemic features Raised inflammatory markers	
Referred lumbar spine pain	Femoral nerve compression may cause referred pain in the hip Femoral nerve stretch test may be positive - lie the patient prone. Extend the hip joint with a straight leg then bend the knee. This stretches the femoral nerve and will cause pain if it is trapped	
Greater trochanteric pain syndrome (Trochanteric bursitis)	Due to repeated movement of the fibroelastic iliotibial band Pain and tenderness over the lateral side of thigh Most common in women aged 50-70 years	
Meralgia paraesthetica	Caused by compression of lateral cutaneous nerve of thigh Typically burning sensation over antero-lateral aspect of thigh	
Avascular necrosis	Symptoms may be of gradual or sudden onset May follow high dose steroid therapy or previous hip fracture of dislocation	
Pubic symphysis dysfunction	Common in pregnancy Ligament laxity increases in response to hormonal changes of pregnancy Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen	
Transient idiopathic osteoporosis	An uncommon condition sometimes seen in the third trimester of pregnancy Groin pain associated with a limited range of movement in the hip Patients may be unable to weight bear ESR may be elevated	

Hip problems in children

The table below provides a brief summary of the potential causes of hip problems in children

Condition	Notes	
Development dysplasia of the hip	Often picked up on newborn examination Barlow's test, Ortolani's test are positive Unequal skin folds/leg length	
Transient synovitis (irritable hip)	Typical age group = 2-10 years Acute hip pain associated with viral infection Commonest cause of hip pain in children	
Perthes disease	Perthes disease is a degenerative condition affecting the hip joints of children, typically between the ages of 4-8 years. It is due to avascular necrosis of the femoral head	
	Perthes disease is 5 times more common in boys. Around 10% of cases are bilateral Features • hip pain: develops progressively over a few weeks • limp • stiffness and reduced range of hip movement • x-ray: early changes include widening of joint space, later changes include decreased femoral head size/flattening	
Slipped upper femoral epiphysis	Typical age group = 10-15 years More common in obese children and boys Displacement of the femoral head epiphysis postero-inferiorly Bilateral slip in 20% of cases May present acutely following trauma or more commonly with chronic, persistent symptoms Features • knee or distal thigh pain is common • loss of internal rotation of the leg in flexion	
Juvenile idiopathic arthritis (JIA)	Preferred to the older term juvenile chronic arthritis, describes arthritis occurring in someone who is less than 16 years old that lasts for more than three months. Pauciarticular JIA refers to cases where 4 or less joints are affected. It accounts for around 60% of cases of JIA Features of pauciarticular JIA ightharpoonup joint pain and swelling: usually medium sized joints e.g. knees, ankles, elbows limp ANA may be positive in JIA - associated with anterior uveitis	
Septic arthritis	Acute hip pain associated with systemic upset e.g. pyrexia. Inability/severe limitation of affected joint	

Lateral epicondylitis

Lateral epicondylitis: worse on resisted wrist extension/suppination whilst elbow extended

Lateral epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow'). It is most common in people aged 45-55 years and typically affects the dominant arm.

Features

- pain and tenderness localised to the lateral epicondyle
- pain worse on wrist extension against resistance with the elbow extended or supination of the forearm with the elbow extended
- episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks

Management options

- · advice on avoiding muscle overload
- simple analgesia
- steroid injection
- physiotherapy

Lower back pain

- Lower back pain (LBP) is one of the most common presentations seen in practice.
- Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.
 - ⇒ musculogenic (strain) etiology is the most common cause of low back pain.

Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- · systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	 May be acute or chronic Pain worse in the morning and on standing On examination there may be pain over the facets. The pain is typically worse on extension of the back
Spinal stenosis	 Usually gradual onset Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. Pain may be described as 'aching', 'crawling'. Relieved by sitting down, leaning forwards and crouching down Clinical examination is often normal Requires MRI to confirm diagnosis
Ankylosing spondylitis	 Typically a young man who presents with lower back pain and stiffness Stiffness is usually worse in morning and improves with activity Peripheral arthritis (25%, more common if female)
Peripheral arterial disease	 Pain on walking, relieved by rest Absent or weak foot pulses and other signs of limb ischaemia Past history may include smoking and other vascular diseases

Flexion (Bending Forward) Extension (Bending Backward)

- (also known as zygapophyseal, apophyseal, or Z-joint)
- are synovial joints between the spinal vertebrae
- Function: guide and limit movement of the spinal motion segment.

Assessment

- Do risk stratification for new cases
 - ⇒ such as the STarT Back risk assessment tool
- do not request imaging unless serious underlying pathology is suspected.

STarT Back Screening Tool

- 1. My back pain has spread down my leg(s) at some time in the last 2 weeks
- 2. I have had pain in the shoulder or neck at some time in the last 2 weeks
- 3. I have only walked short distances because of my back pain
- 4. In the last 2 weeks, I have dressed more slowly than usual because of back pain
- 5. It's not really safe for a person with a condition like mine to be physically active
- 6. Worrying thoughts have been going through my mind a lot of the time
- 7. I feel that my back pain is terrible and it's never going to get any better
- 8. In general I have not enjoyed all the things I used to enjoy
- 9. Overall, how bothersome has your back pain been in the last 2 weeks? Not at all (0), Slightly, (0), Moderately (0), Very much (1), Extremely (1)
- STarT Back scoring:

- ⇒ For questions 1-8, score 1 for agreement, 0 for disagreement
 - Low risk = total score 0-3:
 - high risk = score 4-5 of questions 5-9 only;
 - the rest are medium risk.

Management (NICE: November 2016)

Non-pharmacological

- ⇒ Self-management
 - encouragement to continue with normal activities.
- ⇒ Exercise
- ⇒ Manual therapies (spinal manipulation, mobilisation or soft tissue techniques such as massage)
 - Traction is NOT recommended
- ⇒ Psychological therapy (cognitive behavioural)
- ⇒ Acupuncture and Electrotherapies are NOT recommended

Pharmacological

- ⇒ NSAIDs
- ⇒ Do not offer paracetamol alone for managing low back pain.
- ⇒ Consider weak opioids (with or without paracetamol) for managing <u>acute</u> low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
- ⇒ Do not offer opioids for managing **chronic** low back pain.
- ⇒ Antidepressants and anticonvulsants are not recommended

· Invasive non-surgical treatments

- ⇒ Spinal injections are not recommended for treatment.
 - except for 'radiofrequency denervation'.
 - To determine whether these people will benefit from this procedure, they may be offered a diagnostic block of the nerves that supply the joints between the vertebrae.
 - If they experience significant pain relief they may then be offered radiofrequency denervation in an attempt to achieve longer-term relief

⇒ Radiofrequency denervation

- for chronic low back pain if:
 - 1) non-surgical treatment has not worked and
 - the main source of pain is thought to come from structures supplied by the medial branch nerve and
 - 3) they have moderate or severe pain
- Only performed after a positive response to a diagnostic medial branch block.
- ⇒ epidural injections of local anaesthetic and steroid in people with acute and severe sciatica.

• Invasive surgical treatments:

- ⇒ spinal decompression
 - for sciatica when non-surgical treatment has not improved pain
- ⇒ Spinal fusion and disc replacement are NOT recommended in treatment of low back pain.

Mixed connective tissue disease (MCTD)

Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease

Definition

 MCTD is an overlap syndrome characterised by combinations of clinical features of SLE, systemic scleroderma and polymyositis (e.g. arthralgia, myositis and Raynaud's).

Feature

- The presenting symptoms of MCTD are most often:
 - ⇒ Raynaud's phenomenon
 - ⇒ puffy hands
 - ⇒ arthralgias
 - ⇒ myalgias
 - ⇒ fatigue.

Diagnosis

- Anti-RNP positive
 - ⇒ A defining feature of MCTD is the presence of antibodies against the U1 ribonucleoprotein (U1 RNP) complex, and hence the presence of high titre anti-U1 RNP will confirm the clinical diagnosis of MCTD.

Prognosis

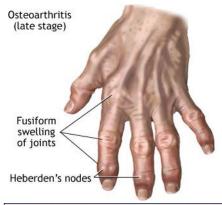
• Most deaths are due to heart failure caused by pulmonary arterial hypertension.

Osteoarthritis

The trapezio-metacarpal joint (base of thumb) is the most common site of hand osteoarthritis

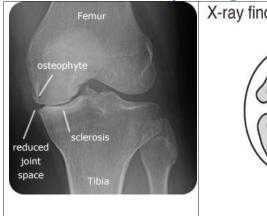
Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

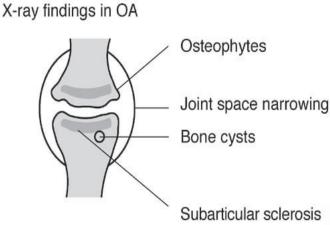
- Pathogenesis involves the localised loss of cartilage, with remodelling of adjacent bone.
- Osteoarthritis characteristically affects the distal interphalangeal as well as the proximal interphalangeal and first metacarpophalangeal joints.
- The carpometacarpal (CMC) joint is classically involved
- Joint swelling is bony in nature, unlike the boggy swelling which occurs in inflammatory arthritis.
- Thenar wasting occurs in OA of the first CMC joint due to disuse.
- pain is exacerbated by exercise and relieved by rest, although in advanced disease rest and night pain can develop.
- Obesity is one of the commonest causes for the early appearance of osteoarthritis
- Osteoarthritis may be secondary to haemochromatosis → do Ferritin



Typical findings in the *hand* are bony enlargement of the proximal interphalangeal joints (Bouchard's nodes) and the distal interphalangeal joints (Heberden's nodes)

Osteoarthritis: x-ray changes





X-ray changes of osteoarthritis

- · decrease of joint space
- subchondral sclerosis
- subchondral cysts
- · osteophytes forming at joint margins

gull-wing or inverted-T pattern of erosions is typical of erosive inflammatory osteoarthritis.

GULL WING SIGN

DIP jts showing central erosions and marginal osteophytes in EROSIVE OSTEOARTHRITIS.





Osteoarthritis: management

Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

NICE recommend co-prescribing a PPI with NSAIDs in all patients with osteoarthritis

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- paracetamol and topical NSAIDs are first-line analgesics. Topical NSAIDs are indicated only for OA of the knee or hand
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intraarticular corticosteroids. A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, Transcutaneous Electrical Nerve Stimulation (TENS) and shock absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis
 reported significant short-term symptomatic benefits including significantly reduced joint
 space narrowing and improved pain scores
- more recent studies have however been mixed
- the 2008 NICE guidelines suggest it is not recommended
- a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

Studies have shown that paracetamol 1 g combined with **codeine at dose of 60 mg** have the best analgesic outcomes.

40 Chapter 8 Rheumatology

The guiding principle in the management of osteoarthritis is to treat the symptoms and disability, not the clinical or radiological appearances. Educating the individual about the disease and its effects reduces pain, distress and disability and increases compliance with treatment. Psychological or social factors after the impact of the disease.

The following table compares osteoarthritis with rheumatoid arthritis.

	OA	RA
Morning stiffness	< 30 minutes	> 1 hour
DIP	Yes	No
PIP	Yes	Yes
MCP	No	Yes
RF, anti-CCP	No	Yes
Joint fluid leukocyte count	< 2,000	5,000-50,000

Osteomyelitis

Osteomyelitis: MRI is the imaging modality of choice

If no other information is available about a patient with osteomyelitis, the causative bacteria is *Staphylococcus aureus* until proven otherwise.

Patients with sickle cell disease have a predisposition to develop osteomyelitis due to *Salmonella* species.

Definition

- · Osteomyelitis: infection of bone marrow and bone
- · Acute form: develops within days or weeks
- Chronic form: develops slowly (over months or years) and is associated with avascular bone necrosis and sequestrum formation within the bone

Causes

- Staph. aureus is the most common cause followed by Pseudomonas
- Pseudomonas aeruginosa is more common in intravenous drug users.
- Salmonella species is the commonest cause in patients with sickle-cell anaemia.
- Pasteurella multocida
 - ⇒ seen in cases caused by cat and dog bites
- Haematogenous osteomyelitis:
 - ⇒ most commonly involves the vertebrae, but infection may also occur in the metaphysis of the long bones, pelvis, and clavicle.
 - The lumbar spine is most commonly affected, followed by the thoracic and cervical regions.
 - ⇒ the location is usually **metaphyseal**
 - The metaphysis is commonest site of osteomyelitis, because:

- Is highly vascular
- Has a hair pin like arrangement of capillaries
- Has sluggish blood flow
- has relatively fewer phagocytic cells than the physis or diaphysis, allowing infection to occur more easily in this area
- thin cortex
- Posttraumatic osteomyelitis
 - ⇒ typically found in the tibia.
- Contiguous-focus osteomyelitis
 - ⇒ direct inoculation of bacteria via trauma
 - ⇒ Infection usually results approximately one month after inoculation.

Predisposing conditions

- · diabetes mellitus
- sickle cell anaemia
- intravenous drug user
- immunosuppression due to either medication or HIV
- alcohol excess

Investigations

- MRI is the imaging modality of choice, with a sensitivity of 90-100%
 - \Rightarrow show \Rightarrow cortical destruction, bone marrow inflammation, soft tissue involvement
- Bone scintigraphy (Gallium bone scan) if MRI is contraindicated (metal foreign body implants) → detects sites of infection
- X-ray shows:
 - ⇒ still provide the best initial **screening** test for acute and chronic osteomyelitis.
 - ⇒ Early stages (< 2 weeks of symptoms onset): typically no pathological findings
 - ⇒ Later stages: bone destruction, **sequestrum** formation, periosteal reactions
 - ⇒ lytic lesion with sclerotic margins (Brodie's abscess)
 - a form of chronic osteomyelitis
 - thickened bone with irregular and patchy sclerosis that gives a honeycombed appearance.
 - Sequestra are seen as dense loose fragments lying within a cavity in the bone.
 - insidious onset (eg: 6-month history of gradually progressive swelling and pain)
 - often near the site of the metaphysis,
 - Deep 'boring' pain is often the predominant symptom.
 - ⇒ Osteomyelitis can cause a raised <u>periosteum</u> which is part of the radiographic sign known as the <u>Codman triangle</u>.
- Bone biopsy
 - ⇒ confirmatory test
 - ⇒ Detects both osteonecrosis and the pathogen → confirms the diagnosis and helps guide more specific therapy



The x ray shows lucent defects in the head of the humerus with loss of the normally well-corticated surface. This is consistent with osteomyelitis.

Differential diagnosis

- Septic arthritis
 - ⇒ Infection of the joint; in contrast to osteomyelitis, <u>involvement of the metaphysis is</u> rare
- Ewing sarcoma
 - ⇒ x-ray: lytic bone lesions, onion skin appearance of the periosteum

Management

- flucloxacillin for 6 weeks
- · clindamycin if penicillin-allergic
- Beta-lactams and vancomycin are commonly used as initial empiric therapy.
- Osteomyelitis from contiguous spread of infection
 - ⇒ Piperacillin-tazobactam
 - ⇒ Patients with penicillin allergy → Clindamycin or metronidazole plus ciprofloxacin
 - ⇒ If MRSA is suspected: → Add vancomycin (or linezolid if allergic to vancomycin).

Skull base osteomyelitis

- Risk factors
 - ⇒ Usually osteomyelitis of the skull is **preceded by a local infection**, for example:
 - Sinusitis extending to the sphenoid sinuses and involving frontal bone may have serious complications such as cavernous sinus thrombosis
 - Mastoid cell infection and occipital bone osteomyelitis
 - Necrotising otitis externa, complicated by petrous bone osteomyelitis with cranial nerve involvement (most common site of skull base osteomyelitis).
 - ⇒ people with compromised immunity (eg: diabetic patient with otitis externa)
- Causative pathogens
 - ⇒ Typically, *Pseudomonas aeruginosa* is the causative pathogen.
 - ⇒ Less common pathogens are *Proteus mirabilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*.
- Features
 - ⇒ The clinical scenario depends on the affected part of the skull base in its most common form, that is, petrous bone involvement.
 - Patients suffer from chronic otitis externa with otalgia and otorrhoea, which, if untreated, progress and cause unilateral headache, cranial nerve palsies, most

commonly IX, X, XI (jugular foramen content) and include also XII nerve form, Villaret's syndrome.

Investigations

- ⇒ The usual biochemical picture is raised erythrocyte sedimentation rate (ESR) and normal white cell count (WCC) and C reactive protein (CRP).
- ⇒ The typical imaging finding are signs of bone destruction especially clivus, shown as hypointensity of bone marrow in the clivus and preclival soft tissue infiltration on MRI T1 weighted images.
- ⇒ **Diagnosis** is **confirmed by** fine needle aspiration (FNA) of tissue and cultures.
- Treatment with antibiotics.

Discitis

- Staphylococcus aureus is the commonest cause of bacterial discitis in adults.
- infection should be considered for patients with a history of fever, weight loss, and non-mechanical back pain (i.e., pain that occurs even without motion, particularly at rest and at night); hx of intravenous drug use, immunosuppression, or diabetes
- localised tenderness present particularly with percussion;
- · neurological findings absent

Differential diagnosis

- epidural abscess
 - ⇒ Unlike discitis, epidural abscess presents with neurological signs in the lower limbs.
- Osteoporotic spinal fracture
 - ⇒ Osteoporotic spinal fractures present with acute pain, however in these patients the plain x ray film demonstrates vertebral collapse.
- Acutely painful spinal metastases are unlikely in the absence of plain film x ray changes.

Osteomalacia

The symptoms of proximal bone pain with hypocalcaemia and low phosphate suggest a diagnosis of osteomalacia

$\downarrow \downarrow$ Ca $\downarrow \downarrow$ P $\downarrow \downarrow$ vit D + $\uparrow \uparrow$ ALP → osteomalacia

Basics

- normal bony tissue but decreased mineral content
- · rickets if when growing
- osteomalacia if after epiphysis fusion
- occurs more commonly in patients of South Asian origin, particularly those who have a cultural tendency to spend more time inside.
- more common in ethnic groups who are dark-skinned, or cover themselves up so that cholesterol cannot be converted to vitamin D in the skin.
- Asians who eat chapattis are also at risk, as the phytic acid in the chapattis chelates vitamin D and calcium
- Europid ethnic origin is associated with a reduced risk of osteomalacia versus populations with increased skin pigmentation.

Causes

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- vitamin D resistant: inherited
- renal failure
- · liver disease, e.g. cirrhosis

- drug induced e.g. anticonvulsants
- Mercury poisoning or any heavy metal poisoning causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.

Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia:
 - ⇒ bone pain, particularly around the hips and lower back,
 - ⇒ fractures.
 - ⇒ muscle tenderness,
 - ⇒ proximal myopathy

Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase as it is released from bone reflecting osteoblastic activity.
- Serum PTH is also usually elevated and normalises gradually on response to treatment.
- There is also acidosis which is caused by the inhibition of phosphate, bicarbonate, and sodium reabsorption by PTH.
- x-ray:
 - ⇒ children cupped, ragged metaphyseal surfaces;
 - adults translucent bands (Looser's zones (Linear areas of low density) (pseudofractures)
 - Looser's zones characterised by low-density bands extending from the cortex inwards in the shafts of long bones.

Treatment

· calcium with vitamin D tablets

May 2013 exam: A 58-year-old woman C/O aches and pains in her bones. Generally weak and lethargic. low calcium, phosphate and vitamin D levels combined with a raised alkaline phosphatase and parathyroid hormone level. What is the most appropriate management?

Start vitamin D3 supplementation (Δ → osteomalacia)

Osteopetrosis

Overview

- also known as marble bone disease
- rare disorder of defective osteoclast function resulting in failure of normal bone resorption
- results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common.
- calcium, phosphate and ALP are normal
- stem cell transplant and interferon-gamma have been used for treatment

Osteoporosis

In osteoporosis, there is decreased bone mass, but mineralization is normal.

Causes

- unknown (95%)
- Advancing age and female sex.
 - ⇒ Prevalence increases from 2% at 50 years to more than 25% at 80 years in women.

Risk factors: the most 'important' ones are risk factors that are used by major risk assessment tools such as FRAX:

- history of glucocorticoid use
- · rheumatoid arthritis
- alcohol excess
- history of parental hip fracture (family history of osteoporotic fracture)
- low body mass index
- current smoking

Other risk factors

- · sedentary lifestyle
- · premature menopause
 - ⇒ Early menarche and late menopause are associated with reduced risk of fracture.
- Caucasians and Asians
- endocrine disorders: hyperthyroidism, hypogonadism (e.g. Turner's, testosterone deficiency), growth hormone deficiency, hyperparathyroidism, diabetes mellitus
- multiple myeloma, lymphoma
- gastrointestinal disorders: inflammatory bowel disease, malabsorption (e.g. Coeliac's), gastrectomy, liver disease
- chronic kidney disease
- · osteogenesis imperfecta, homocystinuria

Risk factors for post-menopausal osteoporosis, include

- Early onset (<45 years) menopause
- Absence of hormone replacement therapy, calcium and vitamin D supplemention and
- · Low body weight.

Medications that may worsen osteoporosis (other than glucocorticoids):

- SSRIs
- antiepileptics
- · proton pump inhibitors
- glitazones
- long term heparin therapy
- aromatase inhibitors e.g. anastrozole (used for breast cancer in postmenopausal women and gynecomastia in men. aromatase, which converts androgens into estrogens by a process called aromatization.)

feature

- Classically, osteoporosis in the absence of fracture, does not cause pain. Many patients
 with osteoporosis have concomitant disorders such as osteomalacia and osteoarthritis
 which cause bone pain.
- Patients with osteoporosis may have no warning signs until the first fracture occurs.
- Gradual height loss and dorsal kyphosis may result from microfractures or complete fractures of vertebral bodies.

Investigations for secondary causes

If a patient is diagnosed with osteoporosis or has a fragility fracture further investigations may be warranted. NOGG recommend testing for the following reasons:

- exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
- identify the cause of osteoporosis and contributory factors;
- assess the risk of subsequent fractures;
- select the most appropriate form of treatment

The following investigations are recommended by NOGG:

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- Thyroid function tests
- Bone densitometry (DXA)

Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
- · Protein immunoelectrophoresis and urinary Bence-Jones proteins
- 25OHD
- PTH
- Serum testosterone, SHBG, FSH, LH (in men),
- Serum prolactin
- 24 hour urinary cortisol/dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)

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- Isotope bone scan
- · Markers of bone turnover, when available
- Urinary calcium excretion

So from the first list we should order the following bloods as a minimum for all patients:

- full blood count
- · urea and electrolytes
- · liver function tests
- · bone profile
- CRP
- · thyroid function tests

DEXA scan

Basics

- T score: based on bone mass of young reference population (compare the patient's bone mineral density (BMD) with that of a healthy young adult)
- T score of -1.0 means bone mass of one standard deviation below that of young reference population
- Z score is adjusted for age, gender and ethnic factors (Z-scores compare the individual's BMD with that of a population of peers)
 - ⇒ The Z-score is not routinely used in the diagnosis of osteoporosis
 - ⇒ It can be used to investigate the possibility of osteoporosis in premenopausal women, men under the age of 50 and children.
 - ⇒ It is most useful when the bone mineral density is less than 2 standard deviations below the normal.

T score

- > -1.0 = normal
- -1.0 to -2.5 = osteopaenia
- < -2.5 = osteoporosis

Osteoporosis diagnosis according to the WHO and International Osteoporosis Foundation criteria:

diagnosis	T score	definition
normal	(≥-1)	hip BMD greater than the 1 SD below the young adult reference mean
osteopaenia	(-1 to -2.5)	hip BMD between 1 and 2.5 DS below the young adult reference mean
osteoporosis	(≤ −2.5)	hip BMD 2.5 SD or more below the young adult reference mean
Severe osteoporosis	(≤ -2.5 PLUS fracture)	hip BMD 2.5 SD or more below the young adult reference mean + one or more fragility fractures

May 2016

What percentage of young adults have a T score between -2.0 to +2.0?



The T score is calculated based on the young adult mean bone density. Given bone density is normally distributed, a T score between -2.0 and +2.0 spans two standard deviations above and below the mean, which covers 95% of the population.

- 5% of young adults lie outside the boundaries of T score 2.0 to +2.0
- 2.5% of young adults have a T score above + 2.0 & 2.5% of young adults have a T score below -2.0
- 99.7% of young adults have a T score between 3.0 to +3.0
- 68% of young adults have a T score between 1.0 to +1.0

Osteoporosis: glucocorticoid-induced

- Steroids cause a decrease in calcium absorption from the gut, increased urinary calcium excretion, and also causes bone resorption, resulting in osteoporosis.
- The risk ↑↑ with prednisolone 7.5mg a day for 3 or more months.
- patients should be managed in an anticipatory, i.e. if it likely that the patient will have to take steroids for at least 3 months then we should start bone protection straight away, rather than waiting until 3 months has elapsed.
- A good example is a patient with newly diagnosed polymyalgia rheumatica. As it is very likely they will be on a significant dose of prednisolone for greater than 3 months bone protection should be commenced immediately.

Management of patients at risk of corticosteroid-induced osteoporosis The RCP guidelines divide patients into two groups.

- 1. age > 65 years **or** H/O previously fragility fracture → give bone protection.
 - ⇒ Fragility fracture defined by The WHO as resulting from a mechanical force equivalent to a fall from standing height or less which should not ordinarily cause a fracture.
- 2. age < 65 years → bone density scan

T score	Management
Greater than 0	Reassure
Between 0 and -1.5 Repeat bone density scan in 1-3 years	
Less than -1.5	Offer bone protection

The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

Osteoporosis: Assessing patients following a fragility fracture

• The management of patients following a fragility fracture depends on age.

Patients ≥ 75 years of age

- Patients ≥ 75 years + fragility fracture → start first-line therapy (an oral bisphosphonate),
 without DEXA scan.
- For example, a 79-year-old woman falls over on to an outstretched hand and sustains a
 Colles' fracture (fracture of the distal radius). Given her age she is presumed to have
 osteoporosis and therefore started on oral alendronate 70mg once weekly. No DEXA scan
 is arranged.
- the 2014 NOGG guidelines have a different threshold, suggesting treatment is started in all women > 50 years who've had a fragility fracture 'although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.'

Patients < 75 years of age

- patient < 75 years + fragility fracture → DEXA scan should be arranged.
- These results can then be entered into a FRAX tool to assess ongoing fracture risk.

Osteoporosis: assessing risk

Osteoporosis in a man - check testosterone

Who should be assessed for fragility fracture?

- all women aged ≥ 65 years and all men aged ≥ 75 years.
- Younger patients + presence of risk factors, such as:

- ⇒ previous fragility fracture
- ⇒ current use or frequent recent use of oral or systemic glucocorticoid
- ⇒ history of falls
- ⇒ family history of hip fracture
- ⇒ other causes of secondary osteoporosis
- ⇒ low body mass index (BMI) (< 18.5 kg/m)
- ⇒ smoking
- ⇒ alcohol (> 14 units/week for women and > 21 units/week for men).

Methods of risk assessment

NICE recommend using a clinical prediction tool such as FRAX or Q Fracture to assess a patient's 10-year risk of developing a fracture. This is analogous to the cardiovascular risk tools such as QRISK.

FRAX

- estimates the 10-year risk of fragility fracture
- valid for patients aged 40-90 years
- based on international data so use not limited to UK patients
- assesses the following factors:
 - 1. age,
 - 2. sex.
 - 3. weight,
 - 4. height,
 - 5. previous fracture,
 - 6. parental fracture.
 - 7. current smoking.
 - 8. glucocorticoids,
 - 9. rheumatoid arthritis,
 - 10. secondary osteoporosis,
 - 11. alcohol intake
- bone mineral density (BMD) is optional, but clearly improves the accuracy of the results.
- NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result

Q Fracture

- · estimates the 10-year risk of fragility fracture
- developed in 2009 based on UK primary care dataset
- can be used for patients aged 30-99 years (this is stated on the Q Fracture website, but other sources give a figure of 30-85 years)
- includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants

DEXA scan

- There are some situations where NICE recommend arranging BMD assessment (i.e. a DEXA scan) rather than using one of the clinical prediction tools:
 - ⇒ before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).
 - ⇒ in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of highdose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).
- Indicators of low BMD are:
 - ⇒ low body mass index (defined as less than 22 kg/m²),
 - ⇒ medical conditions such as ankylosing spondylitis, Crohn's disease,
 - ⇒ conditions that result in prolonged immobility, and
 - ⇒ untreated premature menopause

Interpreting the results of FRAX

- If the FRAX assessment was done without a bone mineral density (BMD) measurement the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:
 - low risk: reassure and give lifestyle advice
 - > intermediate risk: offer BMD test
 - high risk: offer bone protection treatment
- If the FRAX assessment was done with a bone mineral density (BMD) measurement the
 results (10-year risk of a fragility fracture) will be given and categorised automatically into
 one of the following:
 - > reassure
 - consider treatment
 - strongly recommend treatment
- If you use Q Fracture instead patients are not automatically categorised into low, intermediate or high risk. Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture. This data then needs to be interpreted alongside either local or national guidelines, considering certain factors such as the patient's age.

When should we reassess a patient's risk (i.e. repeat the FRAX/Q Fracture)?

- if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, or
- when there has been a change in the person's risk factors

Osteoporosis: management

- secondary prevention of osteoporotic fractures in postmenopausal women (NICE guidelines 2008). Key points include
 - → osteoporotic fragility fractures in postmenopausal women + confirmed osteoporosis
 (a T-score of 2.5 SD or below) → treatment.
 - In women aged ≥ 75 years, a DEXA scan may not be required
 - vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
 - If osteoporosis is established, the treatment includes 1500 mg/day of calcium and 400-800 pg /day of vitamin D
 - Dietary intake of calcium should be:
 - ❖ 800-1000 mg/day in childhood through early adulthood
 - 1000-1200 mg/day in the middle years
 - 1500 mg/day in the elderly

> alendronate is first-line

- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)
- Treatment criteria for patients not taking alendronate: for patients who do not tolerate alendronate, the most important thing to remember is:
 - the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
 - if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)</p>
 - the strictest criteria are for denosumab

Supplementary notes on treatment

- Bisphosphonates
 - ⇒ Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) are recommended for treating osteoporosis only if:
 - the 10- year probability of osteoporotic fragility fracture is at least 1%.
 - ⇒ Intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended for treating osteoporosis only if:
 - the 10- year probability of osteoporotic fragility fracture is at least 10% or
 - the 10- year probability of osteoporotic fragility fracture is at least 1% and the
 person has difficulty taking oral bisphosphonates (alendronic acid, ibandronic
 acid or risedronate sodium) or these drugs are contraindicated or not
 tolerated.
 - ⇒ alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
 - ⇒ reduce the risk of both vertebral and non-vertebral fractures
 - ⇒ alendronate, risedronate may be superior to etidronate in preventing hip fractures
 - ⇒ Alendronic acid
 - tablets, 10 mg once a day
 - tablets, 70 mg once a week
 - ⇒ Risedronate sodium
 - tablets, 5 mg once a day
 - tablets, 35 mg once a week
 - ⇒ Etidronate is an oral bisphosphonate
 - administered in 90-day cycles, with each cycle consisting of etidronate (400 mg/day) for 14 days followed by calcium carbonate (1.25 g/day) for the remaining 76 days.
 - ⇒ Zoledronic acid
 - intravenous infusion, 50 micrograms/ml once a year
 - ⇒ ibandronate is a once-monthly oral bisphosphonate
 - ⇒ Ibandronic acid:
 - tablets, 150 mg once a month
 - injection, 3 mg/ml once every 3 months
 - ➡ Instructions for administration
 - Alendronate and risedronate must be taken with 200 ml and 120 ml of water, respectively.
 - Before and immediately after administration patients should not eat or drink, and must remain upright for stipulated time periods.
 - Etidronate should be taken with water at the midpoint of a 4-hour fast (that is, 2 hours after and 2 hours before food, vitamins with mineral supplements such as iron, calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium).
 - ⇒ contraindicated in patients with a GFR less than 35 ml/min
 - Data from randomised controlled trials supports use of bisphosphonates down to GFRs as low as 30-35 ml/min. Below this level RCT evidence is unavailable, and the risk of adynamic bone disease associated with renal impairment is significantly elevated.
 - ➡ Bisphosphonate induce osteonecrosis of the jaw (associated with dental extraction surgery and increased with underlying malignancy, especially multiple myeloma)
 - Most cases have been associated with zoledronic acid and pamidronate given intravenously for metastatic bone disease.
 - The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
 - Dental disease is a recognised predisposing factor.

 The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.

Vitamin D and calcium

- ⇒ poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures may reduce rates in frail, housebound patients
- Raloxifene selective oestrogen receptor modulator (SERM)
 - (SERMs) are drugs with selective activity in various organ systems, acting as weak oestrogen-receptor agonists in some systems and as oestrogen antagonists in others
 - ⇒ prevent bone loss
 - reduce risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
 - ⇒ increase bone density in the spine and proximal femur
 - ⇒ less effective in preventing loss of bone mineral density versus bisphosphonates or denosumab.
 - ⇒ disadvantages
 - may worsen menopausal symptoms
 - increased risk of thromboembolic events
 - ⇒ contraindicated in:
 - history of venous thromboembolism (VTE),
 - hepatic impairment,
 - cholestasis.
 - severe renal impairment,
 - unexplained uterine bleeding or endometrial cancer.
 - Raloxifene should not be co-administered with systemic oestrogens,
 - in patients with breast cancer it should not be used for osteoporosis treatment or prevention until treatment of the breast cancer, including adjuvant treatment, has been completed.
 - ⇒ advantage:
 - may decrease risk of breast cancer

Strontium ranelate

- ⇒ Action
 - 'dual action bone agent' increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
- ⇒ Indication
 - secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:
 - unable to take alendronate and risedronate due to contraindication, intolerance or unable comply with the special instructions for the administration. And
 - have a combination of T-score, age and number of independent clinical risk factors for fracture (see denosumab indications below).
- ⇒ Dose and administration
 - The dose is 2 g once daily in water, preferably at bedtime.
 - Advice to avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.
 - Treatment with strontium ranelate should be discontinued during treatment with oral tetracycline or quinolone antibiotics.
 - it is not recommended in patients with severe renal impairment
 - should be used with caution in patients at increased risk of VTE.

⇒ Disadvantages

- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- increased risk of cardiovascular events: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- increased risk of thromboembolic events: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

Denosumab

- ⇒ human monoclonal antibody that inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
 - RANK occurs on the surface of osteoclast precursors and osteoclasts.
 Inhibiting it leads to reduced osteoclast formation, function and survival. This leads to reduced bone reabsorption in both cortical and trabecular bone.
- ⇒ given as a single subcutaneous injection every 6 months
 - therefore, tolerated by patients who don't want a daily subcutaneous injection
- ⇒ initial trial data suggests that it is effective and well tolerated
- ⇒ (NICE guidelines 2010) state that: it is recommended only in postmenopausal women at increased risk of fractures:
 - who are unable to comply with alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments and
 - who have a combination of T-score, age and number of independent clinical risk factors for fracture
 - independent clinical risk factors for fracture are:
 - ⇒ parental history of hip fracture.
 - ⇒ alcohol intake of 4 or more units per day, and
 - ⇒ rheumatoid arthritis.
- ⇒ The recommended dosage is 60 mg subcutaneous injection once every 6 months.
- ⇒ Side effects:
 - Like bisphosphonates it is associated with osteonecrosis of the jaw, but not other adverse events such as reflux oesophagitis.
 - The risk of a dynamic bone disease may be less for denosumab versus bisphosphonates because it does not accumulate in bone.

Teriparatide

⇒ is a recombinant fragment of human parathyroid hormone and, as an anabolic agent, it stimulates new formation of bone and increases resistance to fracture.

⇒ Action

- Increased osteoblast activity (the main effect)
- increased calcium absorption from the gut and
- reduced calcium excretion from the kidney.
- □ Indications
 - an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:

- unable to take alendronate and risedronate, or strontium ranelate due to contraindication, intolerance or unsatisfactory response and
- age ≥ 65 years and have a T-score of ≤ -4.0 SD, or a T-score of ≤ -3.5 SD plus more than two fractures, or
- age 55–64 years and have a T-score of ≤ –4 SD plus more than two fractures.

 Although this synthetic parathyroid hormone (PTH) analogue is an effective option for the treatment of severe osteoporosis, it is a <u>daily injectable</u>, and therefore, not considered by many patients, particularly those who don't likely injectables.

⇒ Dose

- The recommended dose is 20 micrograms administered once <u>daily</u> by subcutaneous injection in the thigh or abdomen.
- the maximum total duration of treatment was restricted, by the marketing authorisation, to 18 months.
- ⇒ Contraindications include:
 - pre-existing hypercalcaemia,
 - severe renal impairment,
 - metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of bone),
 - unexplained elevations of alkaline phosphatase, and
 - previous radiation treatment to the skeleton.

Hormone replacement therapy

- ⇒ has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

Hip protectors

- ⇒ evidence to suggest significantly reduce hip fractures in nursing home patients
- ⇒ compliance is a problem

· Falls risk assessment

- ⇒ no evidence to suggest reduced fracture rates
- ⇒ however, do reduce rate of falls and should be considered in management of high risk patients

Raloxifene and teriparatide are second line treatments if bisphosphonates are not tolerated, ineffective or unsuitable for the patient.

(Ref: NICE guidelines . Last updated: 09 August 2017)

Pathophysiology of bone diseases

- Osteoporosis → decreased bone mass, but mineralization is normal.
- Osteomalacia → Decreased bone mineralization (due to vitamin D deficiency)
- Paget's disease → Disorder of bone remodeling (excessive bone resorption, followed by disorganized bone formation occurs, producing thickened but weak bone.)

Paget's disease of the bone

Paget's disease - old man, bone pain, raised ALP

The constellation of bony pain, unilateral hearing loss, and an isolated raised ALP should point you in the direction of Paget's disease of the bone.

Disease localization

- most commonly involves the axial skeleton, the pelvis being the most common, but it can
 affect any area.
- In the majority of patients, the disease affects at least two bones, but in one third of
 patients only one bone is affected.

Epidemiology

- Second most prevalent skeletal disease after osteoporosis
- (UK prevalence 5%) but symptomatic in only 1 in 20 patients
- more common in men (sex ratio 3:2 men: women).
- Age of onset: > 55 years

Pathophysiology

- increased but uncontrolled bone turnover
- It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity.
- it is a focal disorder of bone remodelling characterized by an increase in the number and size of osteoclasts in affected skeletal sites while the rest of the skeleton is spared.
- ↑↑osteoclasts → ↑↑bone resorption → subsequent increase in new bone formation and altered bone architecture.
- The structure of the new bone is disorganised and mechanically weaker and therefore liable to pathological fracture and deformity.

Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

- most commonly no symptoms.
 - ⇒ The diagnosis is typically found incidentally on radiographs and laboratory investigations.
 - ⇒ Paget disease should be considered in an asymptomatic patient who presents with isolated ALP elevation that cannot be explained by any other means (e.g., cholestasis or bone metastases)
 - bone pain (e.g. pelvis, lumbar spine, femur)
 - ⇒ Bone pain is typically increased with rest and on weight bearing.
 - ⇒ Unlike osteoarthritis, pagetic bone pain usually increases with rest, on weight bearing, when the limbs are warmed, and at night.
 - classical, untreated features: bowing of tibia, bossing of skull

Complications

- deafness (cranial nerve entrapment)
 - ⇒ In the skull, the 8th nerve can be compressed, resulting in hearing loss. This is one of the more common complaints, being present in 37% of respondents in a recent survey of 2000 patients with Paget's disease.

- bone sarcoma (1% if affected for > 10 years)
 - ⇒ Although the risk of osteogenic sarcoma is 30 times that of patients without Paget's, the risk of sarcoma development is still small → Less than 1%
 - ⇒ Symptoms of osteogenic sarcoma include increased pain localised to one particular area and pathological fracture.
 - ⇒ tumor arising from mesenchymal stem cells (osteoblasts)
 - ⇒ Most common primary bone malignancy
 - ⇒ x-ray
 - Sunburst appearance of lytic bone lesions and/or codman triangles (a ridge of sub-periosteal new bone is raised by an underlying tumor)
 - □ Treatment
 - Surgery (definitive resection) with adjuvant polychemotherapy
 - usually resistant to radiation therapy
- · Pathological fractures
- Spinal cord compression
- skull thickening
 - ⇒ (A classic symptom: a hat which no longer fits)
- · high-output cardiac failure
 - ⇒ (due to AV shunts in bone)

Diagnosis

- Raised alkaline phosphatase (ALP) calcium* and phosphate are typically normal
 - ⇒ the Best initial test
 - ⇒ * calcium is usually normal but hypercalcaemia may occur with prolonged immobilisation
- X-ray:
 - ⇒ eg: (skull x-ray) thickened vault, osteoporosis circumscripta
 - ⇒ Osteolysis and new bone formation typical of the disease.
 - ➡ Radiographic features in the mixed lytic and sclerotic phase of Paget's disease include:
 - bone expansion,
 - cortical thickening and
 - trabecular bone thickening.
- the best investigation to confirm the diagnosis → Skeletal survey
 - Recent evidence has suggested that limited skeletal survey is superior to bone scan for the assessment of the disease because, when there is significant osteoclastic resorption of bone, bone scanning underestimates the extent of disease activity and still requires plain radiography for confirmation.
- Bone biopsy
 - ⇒ abnormal "mosaic" pattern in woven and lamellar bone.

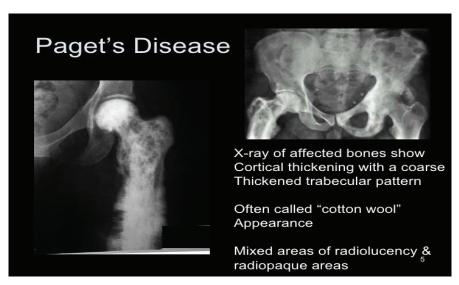
Treatment

- · Indications for treatment include:
 - ⇒ bone pain.
 - ⇒ skull or long bone deformity,
 - ⇒ fracture,
 - ⇒ periarticular Paget's
- The mainstay of treatment for Paget's disease is bisphosphonate therapy, which is
 proven to <u>relieve symptoms of pain</u> and has been shown to <u>reduce the risk of</u>
 pathological fracture in long bones and complications of Paget's such as deafness.
 - > bisphosphonate (either oral risedronate or IV zoledronate)
 - Unless contraindicated, all patients on bisphosphonates should be given supplements of calcium and Vitamin D to avoid symptomatic hypocalcaemia.
 - ⇒ In patients who cannot tolerate these, calcitonin is second-line therapy.
 - calcitonin is less commonly used now

the most appropriate way to monitor disease activity is \rightarrow 6-monthly alkaline phosphatase levels



The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.



Penicillamine

Mechanism of action

- largely unknown
- thought to reduce IL-1 synthesis and prevent the maturation of newly synthesized collagen

Uses

· rheumatoid arthritis

Adverse effects

- rashes
- disturbance of taste
- proteinuria

Pseudogout

Pseudogout - positively birefringent rhomboid shaped crystals

Chondrocalcinosis in a question is most likely to indicate → Pseudogout

Definition

 Pseudogout is a form of microcrystal synovitis caused by the deposition of calcium pyrophosphate dihydrate in the synovium

Risk factors

- · hyperparathyroidism
- hypothyroidism
- haemochromatosis
- · acromegaly
- · low magnesium, low phosphate
- Wilson's disease

Features

- · knee, wrist and shoulders most commonly affected
- · joint aspiration:
 - ⇒ Polar light microscopy: weakly-positively birefringent rhomboid shaped crystals
 - ⇒ Synovial fluid findings: 10,000-50,000 WBCs/µL with > 90% neutrophils
- x-ray: chondrocalcinosis
 - in the large joints, particularly the knees.)

Management

- aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

Psoriatic arthropathy

If first-degree relatives of patients with psoriasis have joint problems, psoriatic arthritis should be considered

- Chronic progressive seronegative inflammatory arthritis occurring in patients with underlying psoriasis.
- most commonly a seronegative oligoarthritis found in patients with psoriasis
 - ⇒ Oligoarthritis (most common, accounting for 70% of cases)
- autoimmune disease, associated with an increased frequency of HLA-B7 and HLA-B27.

Epidemiology

- affects men and women equally
- the range of age of onset between 35–55 years.
- Around 10-20% percent of patients with skin lesions develop an arthropathy

Types

- Five subsets of psoriatic arthritis have been described based on the pattern of joint involvement, with an increased prevalence of the spondylitic form in males and the rheumatoid form in females.
 - 1. asymmetric oligoarthritis (most common) (43%).
 - 2. symmetric polyarthritis (33%)
 - proximal interphalyngeal joint involvement.

- 3. sacroilitis
- 4. DIP joint disease
 - associated with nail pitting, and onycholysis (separation of nail from nail bed)
- 5. arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers') (rare)

The relation between skin lesion and Psoariatic arthritis

- Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions.
 - ⇒ Psoriasis precede psoriatic arthritis in 60-80% of patients (usually by less than 10 years)
 - ⇒ In 15-20% of patients, arthritis appears before the psoriasis
 - Small plagues should be looked for on the elbows and scalp.

Feature

- Psoariatic arthritis tends to affect the distal interphalangeal joints (DIP).
- can present with or without associated psoriatic skin lesions or only with nail malformations.
- If no obvious skin lesions are visible, the clinician must look for psoriasis in hidden sites such as the scalp, intergluteal cleft and umbilicus.
- Nail involvement includes onycholysis, transverse ridging and nail pitting.
- vertebrae may be asymmetrically affected and there may be involvement of the atlantoaxial
 joint with erosion of the odontoid and consequent subluxation.
- Dactylitis with sausage digits is seen in 35% of patients
- Extra-articular features include:
 - ⇒ Ocular involvement may occur in 30% of patients, including:
 - conjunctivitis (in 20%)
 - acute anterior uveitis (in 7%);
 - in patients with uveitis, 43% have sacroiliitis
 - Synovitis affecting flexor tendon sheaths, (with sparing of the extensor tendon sheath)

Investigations

- ↑ (ESR) and C-reactive protein level
- Negative rheumatoid factor
- Low levels of circulating immune complexes (in 56% of patients)
- High Serum immunoglobulin A levels (in two thirds of patients)
- Radiography
 - ⇒ <u>asymmetric</u> "pencil-in-cup" deformity in the <u>distal</u> interphalangeal joints of the fingers.

Diagnostic criteria

- established inflammatory articular disease with at least 3 points from the following features:
 - 1. Current psoriasis (assigned a score of 2)
 - 2. history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
 - 3. **family history of psoriasis** (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
 - 4. Dactylitis (assigned a score of 1)
 - 5. Juxta-articular new-bone formation (assigned a score of 1)
 - 6. RF negativity (assigned a score of 1)
 - 7. Nail dystrophy (assigned a score of 1)

Differential diagnosis

The condition can be distinguished from the sacroilitis seen in ankylosing spondylitis by the
presence of the other clinical signs in the nails and the skin and by differences in the
patterns of vertebral involvement.

- Polyarticular psoriatic arthritis distinguished from rheumatoid arthritis by:
 - 1. presence of dactylitis and
 - 2. absence of anticyclic citrullinated peptide antibodies.

Management

- treat as rheumatoid arthritis but better prognosis
- limited disease → NSAIDs usually sufficient
 - ⇒ do not prevent progressive joint damage
- Patients with progressive peripheral arthritis (polyarthritis, joint erosions) or oligoarthritis refractory to NSAIDs and/or intra-articular corticosteroids require disease-modifying antirheumatic disease therapy (e.g., methotrexate) early in the disease course.
 - ⇒ methotrexate will improve both the joint and skin problems
- Sulfasalazine is safe to use in pregnancy and there is no need to stop it.
 - ⇒ Sulphasalazine tends to only improve joint symptoms and <u>not improve the</u> psoriasis.
- Tumour necrosis factor (TNF)-alpha inhibitors may be considered as <u>second-line</u> therapy for most disease manifestations.
 - ⇒ If not respond to an adequate trial of two DMARDs (for example, leflunomide, methotrexate, sulfasalazine) → anti-TNF agents
- **Apremilast** (Nice guidelines February 2017)
 - ⇒ phosphodiesterase 4 (PDE4) inhibitor.
 - ⇒ ↓anti-inflammatory cytokines and mediators associated with psoriatic arthritis (including [TNF]-alpha and interleukin [IL]-23).
 - ⇒ Apremilast, alone or in combination with (DMARDs), is recommended for psoriatic arthritis only if:
 - they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
 - not responded to adequate trials of at least 2 standard DMARDs.
 - ⇒ Adverse effects
 - (GI) disorders (most commonly diarrhoea and nausea):
 - upper respiratory tract infections;
 - headache; and tension headache.
 - ⇒ Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response
- Hydroxychloroquine → exacerbate psoriatic skin lesions
- In patients with cutaneous psoriasis, systemic corticosteroids predispose to pustular psoriasis, and may result in a flare of skin psoriasis when they are stopped.









X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.



Psoriasis involvement of the nail produces pitting and yellowing, which can be mistaken for onychomycosis.



This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progresion towards a 'pencil-in-cup' changes.

Reactive arthritis (Reiter syndrome)

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

'Can't see, pee or climb a tree'

Urethritis + arthritis + conjunctivitis = reactive arthritis

- Reactive arthritis is defined as an arthritis that develops following an infection where the
 organism cannot be recovered from the joint.
 - ⇒ the presence of bacterial infection on joint aspiration would count against it.
- Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies.
- It encompasses <u>Reiter's syndrome</u>, a term which described a classic triad of urethritis, conjunctivitis and arthritis following a dysenteric illness during the Second World War.
- Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA).

Eye diseases in Reiter's syndrome:

- Most common → conjunctivitis (50%)
- Less common → iritis (12%)

Epidemiology

- post-STI form much more common in men (e.g. 10:1)
- post-dysenteric form equal sex incidence

The table below shows the **organisms that are most commonly associated with reactive arthritis**:

Post-dysenteric form	Post-STI form
Shigella flexneri Salmonella typhimurium Salmonella enteritidis Yersinia enterocolitica Campylobacter	Chlamydia trachomatis

Features

- typically develops within 4 weeks of initial infection
 - ⇒ symptoms generally last around 4-6 months
- arthritis is typically an asymmetrical oligoarthritis of lower limbs
 - ⇒ mainly affecting the large weight-bearing joints (usually knee and ankle).
- dactylitis
- symptoms of urethritis
- eye:

- ⇒ conjunctivitis (seen in 50%),
- ⇒ anterior uveitis
- skin:
 - ⇒ circinate balanitis (painless vesicles on the coronal margin of the prepuce),
 - ⇒ keratoderma blenorrhagica (waxy yellow/brown papules on palms and soles)

Management

- usually self-limiting
- symptomatic: analgesia, NSAIDS, intra-articular steroids
- sulfasalazine and methotrexate are sometimes used for persistent disease

Prevention

- Antibiotics given at the time of the non-gonococcal venereal infection will reduce the likelihood of that person developing reactive arthritis.
 - Appropriate treatment during the acute stage would be doxycycline 100 mg bd if Chlamydia infection is confirmed.

Prognosis

- Prognosis with respect to long-term complications is better when **dysenteric** infection is the precipitant factor rather than **Chlamydial** infection.
- arthritis usually resolves in 3 months
- In general, symptoms last from a few weeks to around 6 months in total.
 - ⇒ symptoms rarely last more than 12 months
- Around 25% of patients have <u>recurrent episodes</u>
- 10% of patients develop chronic disease
- In HLA-B27-positive patients, ankylosing spondylitis may develop in up to 50% of patients who have suffered an episode of reactive arthritis.
- HIV infection is associated with a higher risk of reactive arthritis
 - ⇒ **HLA-B27** is found in 80–90 % of **Caucasians** with HIV-associated reactive arthritis,
 - ⇒ while studies of Africans with HIV-associated reactive arthritis have found nearly all to be HLA-B27-negative
- Rarer long-term complications include:
 - ⇒ urethral stricture.
 - ⇒ cataracts, and
 - ⇒ aortic root necrosis.



Keratoderma blenorrhagica

Amyloidosis

Amyloidosis should always be considered in a patient with a long-standing inflammatory and/or infectious disease who presents with kidney, liver, or GI involvement.

Overview

- amyloidosis is describes the extracellular deposition of an insoluble <u>fibrillar protein</u> termed amyloid
- amyloid also contains a **non-fibrillary protein** called:
 - ⇒ amyloid-P component, derived from the acute phase protein serum amyloid P
 - ⇒ apolipoprotein E
 - ⇒ heparan sulphate proteoglycans
- the accumulation of amyloid fibrils leads to tissue/organ dysfunction

Causes

 Amyloidosis may be inherited or acquired; acquired form is associated with long standing chronic illnesses (DM, Rheumatoid Arthritis).

Feature

- · unexplained weight loss,
- fatigue,
- oedema resistant to diuretic therapy.
- joint pains and stiffness, usually upper limbs more than lower limbs.

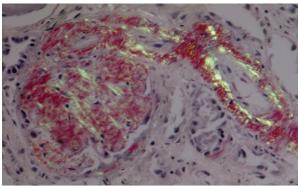
Types

- Light-chain amyloidosis (AL-amyloidosis)
 - ⇒ Most common form of amyloidosis in developed nations
 - ⇒ Aetiology:
 - primary disease caused by plasma cell dyscrasias e.g., :
 - multiple myeloma,
 - Waldenström's macroglobulinemia,
 - non-Hodgkin lymphoma
 - ⇒ Pathophysiology:
 - increased production of the light chains of immunoglobulins → deposition of AL (amyloid light chain) protein in various organs
 - ⇒ Features: rapidly progressive clinical course
 - Heart:
 - restrictive cardiomyopathy,
 - atrioventricular block
 - ⇒ An ECG is required in all patients to look for conduction abnormalities.
 - Kidney:
 - nephrotic syndrome,
 - type II renal tubular acidosis,
 - nephrogenic diabetes insipidus
 - Tongue:
 - macroglossia → obstructive sleep apnea
 - Nervous system:
 - Amyloid peripheral neuropathy
 - ⇒ carpal tunnel syndrome
 - ⇒ only seen in AL, never seen in AA
 - autonomic neuropathy
 - Gastrointestinal tract:
 - malabsorption
 - periorbital ecchymoses
 - Enlargement of the submandibular salivary glands

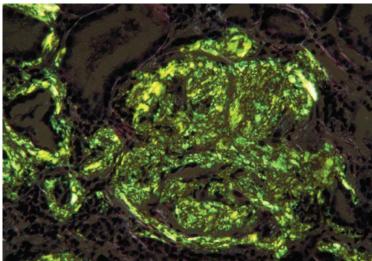
- shoulder pad sign due to periarticular infiltration with amyloid and pseudohypertrophy is specific for AL
- Bleeding disorders
- Reactive amyloidosis (AA-amyloidosis)
 - ⇒ Etiology: secondary disease
 - Chronic inflammatory conditions (e.g., IBD, rheumatoid arthritis, SLE, vasculitis)
 - Chronic infectious diseases (e.g., tuberculosis, bronchiectasis, leprosy, osteomyelitis)
 - Certain tumors (e.g., renal cell carcinoma, lymphomas)
 - ⇒ Pathophysiology:
 - chronic inflammatory process → increased production of acute phase reactant SAA (serum amyloid-associated protein) → deposition of AA (amyloid-associated) protein in various organs
 - ⇒ Clinical features
 - Kidney: most common feature → renal involvement
 - nephrotic syndrome,
 - type II renal tubular acidosis,
 - nephrogenic diabetes insipidus
 - Adrenal glands:
 - primary adrenal insufficiency
 - Liver and spleen:
 - hepatomegaly, splenomegaly
 - Gastrointestinal tract:
 - malabsorption
- β-2 microglobulin amyloidosis
 - Precursor protein is β-2 microglobulin, part of the major histocompatibility complex
 - ⇒ Associated with patients on renal dialvsis
 - ⇒ neurological impairment in patients on longstanding dialysis.

Diagnosis

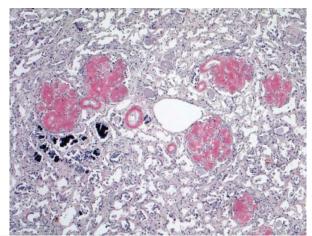
- Biopsy
 - Biopsy of abdominal wall fat, the **rectum** or a salivary gland can be examined
 - ⇒ The tissue is treated with Congo red stain → the amyloid proteins appear apple-green birefringence on Light microscopy.
- Tests to diagnose the underlying disease
 - ⇒ Light chain amyloidosis
 - Serum electrophoresis: → monoclonal gammopathy
 - Urine test for Bence-Jones proteins → multiple myeloma
 - ⇒ Reactive amyloidosis: → ESR, CRP, chest x-ray



Renal amyloid with congo red staining - apple-green birefringence



Renal amyloid with congo red staining - apple-green birefringence



Congo red staining. Amyloid deposits are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy

Pathological feature of amyloidosis

- 1. Electron micrography fibrillar appearance
- 2. x Ray diffraction pattern beta pleated sheet structure
- 3. Haematoxylin and eosin staining amorphous eosinophilic appearance
- 4. Congo red histological staining apple-green birefringence
- 5. Solubility in water and buffers of low ionic strength.

Treatment

- The only treatment is renal transplantation.
- It can be reduced by using high flux dialysis membranes in patients who are likely to be on dialysis for a prolonged period.

Amyloidosis: cardiac

- Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy, associated with AL Amyloidosis
- Presentation: Typical presentation of right heart failure:
 - ⇒ Jugular venous distension
 - ⇒ Peripheral oedema
 - ⇒ Orthopnoea and paroxysmal nocturnal dyspnea are typically absent

Diagnosis

- ⇒ Combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.
- ⇒ Echocardiographic abnormalities include:
 - dilatation of atria, thickened interatrial septum, diastolic dysfunction and smallvolume ventricles.
 - The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases.
 - Cardiac amyloidosis is associated with a 'global speckled' pattern on echo.



The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudoinfarction pattern).

Management of AL

- The most effective treatment is autologous bone marrow transplants with stem cell rescues. However, many patients are too weak to tolerate this approach
- Other treatments can involve application of chemotherapy similar to that used in multiple myeloma. A combination of bortezomib and dexamethasone has been proposed, as has melphalan and dexamethasone.
- Digoxin is contraindicated in cardiac amyloidosis (restrictive cardiomyopathy)

Septic arthritis

Septic arthritis - most common organism: Staphylococcus aureus

Septic arthritis: IV flucloxacillin

Causes

- most common organism overall is Staphylococcus aureus
 - ⇒ The most likely organisms are staphlococci (70%) and beta-haemolytic streptococci (20%).
- in young adults who are sexually active Neisseria gonorrhoeae should also be considered
- The most likely organism to have been aspirated from the infected hip joint replacement prosthesis → Propionibacterium acnes (PA):
 - ⇒ Gram positive bacilli,

- ⇒ it is poorly virulent,
- ⇒ symptoms of PA infection may occur many years after original arthropathy,
- ⇒ it is sensitive to penicillins, clindamycin and carbapenems.

Feature

- Fifty percent of cases will have an associated bacteraemia.
- Early x-rays are almost always normal.

Management

- synovial fluid should be obtained before starting treatment
- intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic
- antibiotic treatment is normally be given for several weeks (BNF states 6-12 weeks)
 - ⇒ ideally these should be intravenous for 2 weeks and then oral for 4 weeks.
- · needle aspiration should be used to decompress the joint
- surgical drainage may be needed if frequent needle aspiration is required
- if patient on warfarin, what is the most appropriate management of anticoagulation before joint aspiration and injection?
 - ⇒ If INR is within the therapeutic range → no need to stop the warfarin or change the dose.
 - ⇒ The risk of a thrombotic episode if anticoagulation is changed outweighs any risk associated with injecting joint while taking anticoagulation.

The following table compares synovial fluid cell count values.

Normal	Inflammatory (Gout/Pseudogout)	Infectious
< 2,000 WBCs	2,000-50,000 WBCs	> 50,000 WBCs

Sjogren's syndrome

- Sjogren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces.
- It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset.
- primary Sjögren's syndrome occurs alone and more likely to have positive anti Ro SSA antibodies than secondary Sjögren's).
- Hypergammaglobulinaemia is present in 80% of individuals.
- Typically secondary Sjögren's has pre-existent rheumatoid or systemic lupus erythematosus before the development of Sjögren's symptoms.
- more common in females (ratio 9:1).
- There is a marked increased risk of lymphoid malignancy (40-60 fold)

Features

- dry eyes: keratoconjunctivitis sicca
- dry mouth
- vaginal dryness
- arthralgia
- Raynaud's.
- myalgia
- sensory polyneuropathy
- renal tubular acidosis (usually subclinical)
- · Plasma cell infiltration of salivary and lacrimal glands: Parotid swelling.

Complication

- · higher risk of developing lymphoma
 - ⇒ These lymphomas are primarily of B cell origin.
 - ⇒ High risk factors for lymphoma development in Sjogren's syndrome patients include:
 - persistent unilateral or bilateral parotid gland enlargement,
 - splenomegaly and lymphadenopathy,
 - low C4 complement levels,
 - type 2 mixed cryoglobulinaemia

Investigation

- rheumatoid factor (RF) positive in nearly 100% of patients
- ANA positive in 70%
- anti-Ro (SSA) antibodies in 70% of patients with PSS
 - Anti-Ro antibody is associated with:
 - congenital complete heart block
 - neonatal lupus
 - The mother is usually positive for anti-Ro or anti-La antibodies but may not have overt lupus erythematosus.
- anti-La (SSB) antibodies in 30% of patients with PSS
- Hypergammaglobulinaemia (↑ IgG) in 80%
- low C4
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
 - ⇒ placement of a standard strip of filter paper on the inside of the lower eyelid.
 - ⇒ Wetting of less than 5 mm in 5 min indicates defective tear production.
- Rose Bengal staining of the eyes commonly shows punctuate or filamentary keratitis.
- histology: focal lymphocytic infiltration
- the most definitive test for Sjögren's syndrome → Labial gland biopsy

Management

- artificial saliva and tears
- pilocarpine may stimulate saliva production

Other causes of dry eyes, and/or dry mouth include:

- past head and neck radiation
- hepatitis C infection
- · acquired immunodeficiency disease
- pre-existing lymphoma
- sarcoidosis
- graft versus host disease, or
- · the use of an anticholinergic drugs.

Systemic lupus erythematosus (SLE)

SLE - antibodies associated with congenital heart block = anti-Ro

SLE: C3 & C4 low

• Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder.

Epidemiology

- much more common in females (F:M = 9:1)
- more common in Afro-Caribbeans* and Asian communities

- ⇒ *It is said the incidence in black Africans is much lower than in black Americans the reasons for this are unclear
- · onset is usually 20-40 years

Pathophysiology

- · autoimmune disease
- associated with HLA B8, DR2, DR3
- thought to be caused by immune system dysregulation leading to immune complex formation
- · the most likely immunopathological process:
 - ⇒ Activation of the classical complement pathway
 - complement consumption is common in active SLE (indicated by the low C3 and C4).
 - Activation of the classical complement pathway occurs in (SLE) owing to the large number of double-stranded DNA (dsDNA) and other immune complexes that form and fix complement.
 - These immune complexes deposit in the kidneys and other organs, where they attract other components of the immune system that cause tissue damage.
- immune complex deposition can affect any organ including the skin, joints, kidneys and brain
- SLE can also be described as a type III hypersensitivity reaction

Features

The triad of fever, arthralgia and rash in a woman of childbearing age should suggest the diagnosis of systemic lupus erythematosus (SLE).

General features

The multisystem presentation of fever, arthralgia, pericarditis and nephritis associated with the epidemiological clues (a young black female) suggest a diagnosis of (SLE).

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

Skin



Malar Rash

- malar (butterfly) rash: spares nasolabial folds
- discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- · photosensitivity
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

Musculoskeletal

- arthralgia typically affecting the small joints of the hands, wrists and knees.
- non-erosive arthritis

Jaccoud's Arthropathy



- <u>Jaccoud's arthropathy</u> → gross deformities of the hands without joint damage or erosions
- caused by recurrent episodes of synovitis that damage tendon sheaths and slings resulting in joint deformity
- seen in:
 - ⇒ SIF
 - ⇒ Rheumatic fever
 - ⇒ Parkinson's disease, and
 - ⇒ Hypocomplementaemic urticarial vasculitis.

Cardiovascular

myocarditis

Respiratory

- pleurisy
- · fibrosing alveolitis
- Direct pulmonary involvement in (SLE) occurs in 30% (pleuropericarditis, atelectasis, pneumonitis, raised hemidiaphragms and **pulmonary fibrosis**).

Renal

- proteinuria
- glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type)

Neuropsychiatric

- · anxiety and depression
- psychosis
- seizures

Investigations Immunology

SLE: ANA is 99% sensitive - anti-Sm & anti-dsDNA are 99% specific

SLE - antibodies associated with congenital heart block = anti-Ro

- 99% are ANA positive (the best screening test for SLE)
 - ⇒ Almost all patients with SLE have a positive ANA test result.
 - ⇒ ANA test is sensitive but not specific for SLE.
 - ⇒ A negative result argues strongly against a diagnosis of active SLE, but does not exclude the possibility of other autoimmune diseases.
 - Negative ANA has the highest negative predicted value (The highest negative predicted value implies the test with the greatest sensitivity.)
- 20% are rheumatoid factor positive
- anti-dsDNA: highly specific (> 99%), but less sensitive (70%)
- anti-Smith: most specific (> 99%), sensitivity (30%)
 - ⇒ Therefore, absence of anti-DNA or anti-Sm antibodies should not exclude SLE as a diagnosis
- also: anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La)
 - ⇒ Anti-Rho and -La antibodies are associated with the development of neonatal lupus.
 - ⇒ Anti-Ro/SS-A antibodies are found in 30% of patients with SLE.
 - ⇒ Anti-Ro antibodies can cross the placenta to cause transient cutaneous lupus in the neonate (5-25% of babies) or permanent congenital heart block (1-3% of babies).

Markers of SLE disease activity

- Early markers of SLE disease activity include:
 - ⇒ falling C₄ levels,
 - although congenital C₄ deficiency is itself a predisposing factor for SLE development, so these tests must be interpreted with caution.
 - ⇒ rising immunoglobulins,
 - ⇒ falling haemoglobin (Hb), white cell count (WCC), platelets and albumin.

Monitoring

- ESR: during active disease the CRP is characteristically normal a raised CRP may indicate underlying infection
- complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement)
- anti-dsDNA titres can be used for disease monitoring (but note not present in all patients)

Management

- Basics
 - ⇒ NSAIDs
 - ⇒ sun-block
- Hydroxychloroquine
 - ⇒ useful for skin disease
- If internal organ involvement e.g. renal, neuro, eye then consider prednisolone, cyclophosphamide

Complication

- Lupus patients are more prone to infection.
 - ⇒ Up to two-thirds of lupus patients will have some lung involvement during the course of their disease. The most common manifestations are pleuritis and pleural effusions.

SLE: pregnancy

Overview

- Unlike many autoimmune diseases (SLE) often becomes worse during pregnancy and the puerperium
- risk of maternal autoantibodies crossing placenta
- leads to condition termed neonatal lupus erythematous
- neonatal complications include congenital heart block
- strongly associated with anti-Ro (SSA) antibodies

Treatment

- azathioprine
 - A large body of evidence from the use of azathioprine in pregnancy for the treatment of both rheumatological conditions and inflammatory bowel disease, supports it's use.
 - ⇒ Although it is less effective in the management of SLE with renal disease versus other options, balance of benefit risk makes it the preferred intervention.
- Ciclosporin
 - ⇒ appears to be associated with premature delivery and low birth weight,
 - ⇒ although it does not seem to be associated with malformations, this drives it's use as an alternative to azathioprine in patients who fail to gain control of their disease.
- Cyclophosphamide, methotrexate and mycophenolate are all contraindicated for use in pregnancy.

Drug-induced lupus erythematosus

Overview

- The pathogenesis of drug-induced lupus is unclear.
- Factors that influence drug metabolism, such as acetylator status, have been implicated.
- In addition, lupus-inducing drugs have been shown to generate a variety of cytotoxic products on exposure to **MPO** released from activated neutrophils.

Epidemiology

- Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans, whereas the inverse is true of idiopathic SLE.
- affect the 50-70-year age group most commonly,
- has a male: female ratio of 1:1

Causes

The most commonly associated drugs

- procainamide
- hydralazine 2,
- quinidine.
- Isoniazid (INH) low risk
- · Sulfasalazine low risk.
- Carbamazepine
- Phenytoin
- Lamotrigine
- anti-TNF alpha agents,
- Interferons
- Statins
- minocycline.
 - ⇒ Minocycline associated with the development of long term immunological memory, and therefore exacerbation of symptoms within 12-24 hours of rechallenge.

Risk factors

- strongly positive ANA
- HLA-DR4 phenotype (hydralazine-induced disease)
- slow acetylator status
 - ⇒ Slow acetylators have increased risk of isoniazid-induced peripheral neuropathy, and hydralazine or procainamide-induced systemic lupus erythematosus (SLE).
- · large total daily doses of precipitating drugs

Features

- symptoms are said to appear some 3 weeks to 2 years after the onset of therapy
- In drug-induced lupus not all the typical features of SLE are seen, with <u>renal and nervous</u> system involvement being unusual.
- Lack of cutaneous involvement
 - ⇒ presents with purpuric, erythematous, papular rash. They do not have a malar or discoid rash.
 - ⇒ skin (e.g. malar rash) (seen in 25%)

- ⇒ However, drug induced lupus due to <u>interferon</u> and due to <u>anti-TNF α agents</u>, may present with malar or discoid rash, and may be anti-dsDNA antibody positive.
- · joint pains, myalgia and malaise are more common
- pulmonary involvement (e.g. pleurisy) are common
- Raynaud's is seen in around 25%

Laboratory features

- ESR and C reactive protein (CRP) are both markedly elevated,
- ANA is strongly positive (in 100%,)
- hypergammaglobulinaemia.
- Anti-dsDNA antibodies are usually negative;
 - ⇒ positive for anti-ssDNA antibody and typically negative for anti-dsDNA antibody.
- antihistone antibodies are positive in 95% of drug-induced lupus (but also 50-80% of idiopathic SLE3).
- anti-Ro, anti-Smith positive in around 5%
- C3/C4 levels are usually normal.

There are several features which distinguish drug-induced lupus from idiopathic SLE:

- Males and females are equally affected in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently.
- Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans, whereas the inverse is true of idiopathic SLE.
- the age of onset is typically older in drug-induced lupus, but this depends on the age at drug exposure.
- Fever, arthralgia, serositis and ANA occur at least as frequently in drug-induced lupus as idiopathic SLE.
- Haematological, renal and central nervous system (CNS) involvement, and double-stranded DNA autoantibodies are rare.

Treatment

- Typically, no further treatment is required after Withdrawal of the precipitating drug
- However, there are situations where corticosteroids or disease modifying antirheumatic drugs (DMARDs) are required to aid resolution.
- The time taken for symptoms to resolve after stopping minocycline is highly variable, from a few days to two years.

Prognosis

Spontaneous recovery usually occurs promptly



A woman with drug-induced lupus

drugs that induce lupus do not need to be avoided in the idiopathic type of lupus.

MRCPUK-part-2-march-2018: A female diagnosed with epilepsy, suffering from an erythematous rash over sun-exposed areas of her skin. Antihistone antibodies are positive. Which medication is the most likely cause of her rash?

→ Phenytoin, carbamazepine and lamotrigine are associated with drug-induced lupus erythematosus

Antiphospholipid syndrome

- Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia.
- It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)
- A key point for the exam is to appreciate that antiphospholipid syndrome causes a
 paradoxical rise in the APTT. This is due to an ex-vivo reaction of the lupus
 anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

Features

- · venous/arterial thrombosis
- recurrent fetal loss
- livedo reticularis
- thrombocytopenia
- prolonged APTT
 - (raised aPTT which fails to correct after the addition of normal human plasma).
- · other features:
 - ⇒ pre-eclampsia,
 - ⇒ pulmonary hypertension
 - ⇒ False positive VDRL testing

Associations other than SLE

- · other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

Risk factor for thrombosis

 Lupus anticoagulant is the greatest predictor of future thrombosis in patients with anti-phospholipid syndrome

Diagnosis

antiphospholipid antibody syndrome (APAS) can be diagnosed if:

- ⇒ the patient has anticardiolipin antibodies, or lupus anticoagulant on two occasions, over a period of 12 weeks,
- ⇒ and either:
 - has had a thrombus, or
 - a history of recurrent < 10-week pregnancy loss, or one pregnancy loss > 10
 weeks in gestation when other causes of pregnancy loss have been excluded.
- Antibodies
- the most clinically important autoantibodies directed against phospholipid binding plasma proteins are:
 - 1. The lupus anticoagulant
 - 2. Anti-beta-2 glycoproetin I antibodies, and
 - 3. The anticardiolipin antibodies.

Management - based on BCSH guidelines

- initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
 - Other opinion: The occurrence of even a single thrombotic event in a patient with antiphospholipid syndrome warrants lifelong anticoagulation, as the risk of recurrence is 20-70%.
- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3.

DD of a significantly prolonged APTT):

- 1. Factor deficiency (factor VIII deficiency, factor IX deficiency and von Willebrand)
- 2. factor VIII inhibitor
 - factor VIII inhibitors are usually time dependent. As a result, when the initial 50:50 mix is done there is correction of the APTT; but if you repeat the APTT after allowing the 50:50 mix to incubate for two hours, there will be no correction.
- 3. presence of lupus anticoagulant (LAC)
 - Coagulation tests to demonstrate the presence of the LAC are as follows:
 - Prolongation of a phospholipid-dependent coagulation test, for example, APTT, kaolin clotting time or others.
 - Demonstration of inhibitor by failing to correct the above coagulation test on 50:50 mixing studies by more than 50%.
 - prolonged (APTT), which does not correct by a significant amount when patient's plasma is mixed with normal plasma.
 - Demonstrate phospholipid dependence-correction of the coagulation test used in (1) with phospholipid.

Antiphospholipid syndrome: pregnancy

Antiphospholipid syndrome in pregnancy: aspirin + LMWH

Antiphospholipid syndrome: (paradoxically) prolonged APTT + low platelets

Antiphospholipid syndrome: arterial/venous thrombosis, miscarriage, livedo reticularis

- Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia.
- It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

In pregnancy the following complications may occur:

- · recurrent miscarriage
- IUGR
- · pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold.

Juvenile idiopathic arthritis (JIA) (Still's disease)

Definition

 The ACR criteria define juvenile rheumatoid arthritis (JRA) by age limit (< 16 y) and the duration of disease (> 6 weeks).

Epidemiology

- the most common form of arthritis in children and adolescents.
- Prevalence: 1/1000 children
- Sex: ♀ > ♂

Types

- Oligoarticular JIA
 - ⇒ Most common form (accounts for 50% of all JIA cases)
 - ⇒ affects four joints or fewer during the first 6 months,
 - ⇒ has the highest risk of developing Chronic anterior uveitis (up to 25%)
 - Bilateral eye involvement is common
 - ⇒ RF negative
 - ⇒ ANA positive (~ 70% of cases)
 - □ Treatment
 - NSAIDs
 - Possibly intra-articular steroid injections
 - Possibly methotrexate

Polyarticular JIA

- ⇒ 40% of cases
- characterised by inflammatory arthritis affecting five or more joints during the first 6 months of the disease.
- ⇒ RF negative
- ⇒ ANA positive (~ 40% of cases)
- ⇒ Treatment: Standard therapy with methotrexate and NSAID
- Systemic-onset JIA (Still's disease)
 - ⇒ < 10% of cases
 </p>
 - presents with fever, arthritis and at least one of the following:
 - erythematous rash,
 - generalised lymphadenopathy,
 - Hepatosplenomegaly
 - serositis (including pleural and pericardial effusions)

- ⇒ RF negative
- ⇒ ↑ Acute phase reactants (e.g., CRP, ferritin)
- ⇒ Treatment: Poor response to methotrexate and TNF inhibitors (etanercept, adalimumab)

Risk factors

. Exposure to antibiotics during childhood may increase the risk of JIA.

Features

Joint pain, daily spiking fevers, and a 'salmon-pink' rash are classic symptoms.

- persistent non-tender joint swelling → (The cardinal feature)
 - ⇒ The first manifestation of JIA is often **limping**, especially in young children.
 - ⇒ The persistent swelling most often occurs in the large joints.
 - \Rightarrow Damage to joints is associated with a $\underline{\mathsf{T}_{H}1}$ response.
- Up to 25% of patients have a **positive anti-nuclear antibody**.
- microcytic anaemia which tends to be resistant to iron replacement
- pericarditis is often found.
- hepatosplenomegaly,
- JIA can decrease bone mass and increase the risk of osteoporosis.
- † ESR (usually seen with all forms of JIA).
- Rheumatoid nodules and rheumatoid factor are usually absent
 - Rheumatoid factor (RF) is absent in most cases of JIA except seropositive polyarticular JIA.
- · anterior uveitis
 - What eye condition is most commonly associated with this presentation? anterior uveitis.
 - about 30–50% of children with JIA have uveitis at diagnosis, especially those who are antinuclear antibody (ANA) positive.
 - The uveitis is typically asymptomatic at onset and must be screened for with an ophthalmologic slit lamp examination.
 - Untreated uveitis can be associated with cataracts, glaucoma and macular oedema
 - about 50–70% of people with severe uveitis develop visual impairment.
 - If a patient with (JIA) developed new-onset anterior uveitis despite treatment with subcutaneous methotrexate → adalimumab (as adalimumab is more effective in treating uveitis than etanercept)

Treatment

- Options for pharmacotherapy include NSAIDs, corticosteroids, methotrexate, and anti-TNF biologicals.
- Treatment with IL-6 receptor antibody has proved to be successful.
- As per NICE guidance, if patient had not responded to methotrexate and should be considered for biologic therapy with either adalimumab, etanercept or tocilizumab.

Prognosis

- Anti-CCP antibodies indicate a poor prognosis.
- Early disease onset is associated with a greater degree of growth impairment and deformity.

Adult onset Still's disease (AOSD) (Adult Still's disease)

Adult-onset Still's disease →triad of persistent high spiking fevers, joint pain, and a distinctive salmon-colored bumpy rash.

typically affects 16-35-year olds

Features

- arthralgia
- rash: salmon-pink, maculopapular (most prominent with fever)
 - ⇒ occurs in approximately 90% of patients
 - ⇒ often seen only when the patient is febrile and is easily missed.
- pyrexia (> 39°C) especially in the afternoon and evening
 - ⇒ described as quotidian or diquotidian returning to 37°C or below between episodes.
- lymphadenopathy
- Hepatosplenomegaly,
- There is often an accompanying sore throat and myalgia.

Rarely there may be:

- · Aseptic meningitis
- Cranial nerve palsies
- Iritis, and
- · Peripheral neuropathy.

Investigation

- neutrophilic leukocytosis, thrombocytosis,
- † serum ferritin
 - ⇒ High serum ferritin, with low glycosylated fraction, are characteristic and can be used as disease activity markers.
- † ESR and C-reactive protein.
- Interleukin (IL)-1, IL-6, IL-18, macrophage colony stimulating factor, interferon gamma and TNF-alpha are all elevated.
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

Diagnosis

 Diagnosis is clinical, and should include exclusion of infectious disease, neoplasms and other autoimmune disease.

Treatment

- non-steroidal anti-inflammatory drugs (NSAIDs),
- corticosteroids.
- disease-modifying anti-rheumatic drugs
- · biological agents.
- Intravenous immunoglobulin may have a role.

Prognosis

• tends to be better when systemic symptoms predominate.

Adult onset Still's disease is typically rheumatoid factor negative

Raynaud's

Raynaud's disease (i.e. primary) presents in young women with bilateral symptoms

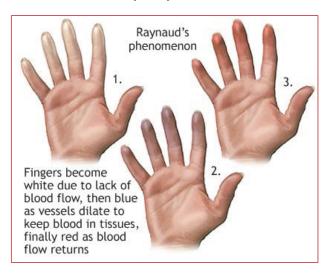
Definition

 Raynaud phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure.

Types

- Primary Raynaud phenomenon (Raynaud disease).
 - Raynaud disease is characterized by the occurrence of the vasospasm alone, with no association with another illness.
 - Raynaud's disease typically presents in **young women** (e.g. 30 years old) with **symmetrical attacks**
 - Around 2% of women and 6% of men with Raynaud's phenomenon develop systemic sclerosis.
 - ⇒ Diagnosis: Primary Raynaud's can be diagnosed if all the following are present:
 - Attacks triggered by exposure to cold and/or stress
 - No suspicion of underlying disease
 - Symmetrical episodes affecting both hands, but not necessarily all fingers
 - No tissue necrosis, ulceration, gangrene or severe ischaemia
 - Normal nail-fold capillaries (Normal capillaroscopy findings)
 - Normal ESR and negative anti-nuclear antibodies.
- · Secondary Raynaud phenomenon
 - ⇒ Secondary causes
 - connective tissue disorders:
 - scleroderma (most common) (90%)
 - mixed connective-tissue disease (85%)
 - rheumatoid arthritis
 - SLE
 - leukaemia
 - Hyperviscosity: polycythemia, paraproteinemias (plasmacytoma, Waldenstrom's disease), cryoglobulinemia, cold agglutinin disease
 - use of vibrating tools
 - Vasculitides: e.g., Buerger's disease
 - cervical rib
 - drugs:
 - oral contraceptive pill,
 - ergot
 - methysergide (for intermittent migraine)
 - beta-blockers
 - vinblastine
 - bleomycin
 - ⇒ Factors suggesting underlying connective tissue disease
 - onset after 40 years
 - Episodes lasting in excess of one hour
 - episodes of secondary Raynaud's are longer
 - Episodes of primary disease typically terminate within 15 minutes following warming in, but can often be prolonged in secondary disease.
 - unilateral symptoms
 - rashes

- presence of autoantibodies
- features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages
- digital ulcers,
- calcinosis
- very rarely: chilblains



Investigations

Which investigation would be most useful in determining whether the Raynaud's is related to vasculitis? → Nail fold capillaroscopy

- The most useful initial assessment must include nail fold capillary loop examination.
 - ⇒ ideally by capillaroscope or, if not available, by ophthalmoscope using magnification.
 - method
 - Nailfold capillaroscopy is performed by applying a drop of oil onto the periungual region of the nail and using an ophthalmoscope set to 40 diopter to examine.
 - interpretation
 - ❖ Patients with connective tissue disorder such as systemic sclerosis most often will show → dilated, distorted, paucity or missed nail fold capillary loops.

Management

- For primary Raynaud phenomenon:
 - ⇒ First line → lifestyle measures.
 - The best initial line
 - Advise on lifestyle changes to reduce the frequency of the attacks, such as heated gloves, stopping smoking and avoiding the cold environments
 - ⇒ Second line → pharmacologic treatment.
 - First pharmacologic line: calcium channel blockers e.g. nifedipine
 - IV prostacyclin infusions:
 - effects may last several weeks/months
 - indications
 - if the patient does not respond to nifedipine Retard or

- ⇒ has developed digital ulceration or ischaemia
- iloprost is a synthetic analogue of prostacyclin
 - The urgent treatment of severe Raynaud's with threatened or established gangrene is with intravenous iloprost.
- ⇒ Third line → non-pharmacologic treatment.
 - Digital sympathectomy should be considered as a last resort when drug therapy has failed or has not been tolerated.
- For secondary Raynaud phenomenon:
 - ⇒ Treatment of underlying disorder
 - ⇒ ACE inhibitors also have the best evidence for <u>reno-protection</u> where <u>there is</u> <u>underlying autoimmune pathology</u>.
 - If there is NO underlying autoimmune pathology → ACEi has NO benefit
 - ACE inhibitors and anti-platelet agents have been trialled in small case series, although no definitive benefit has yet been shown.

Systemic sclerosis (SSc)

- Systemic sclerosis is a chronic autoimmune disease characterised by increased <u>fibroblast</u> activity and fibrosis in a number of different organ systems.
- characterised by hardened, sclerotic skin and other connective tissues.

Epidemiology

- It is four times more common in females ($\mathcal{L} > \mathcal{L}$)
- Higher incidence in African Americans
- Peak incidence: 30-50 years

Types: There are three patterns of disease:

1. Limited cutaneous systemic sclerosis

Limited (central) systemic sclerosis = anti-centromere antibodies

- The more common type of SSc.
- · Raynaud's may be first sign
 - ⇒ seen in 90-95% of patients with systemic sclerosis.
- scleroderma affects face and distal limbs predominately
 - ⇒ Areas of skin affected include only the face, forearms and lower legs up to the knee.
 - ⇒ It does not affect the upper arms, upper legs, or trunk.
- · associated with anti-centromere antibodies
- Previously known as CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia)
 - ⇒ the most likely cause of this patient's dysphagia? → Esophageal smooth muscle atrophy and fibrosis
- Pulmonary hypertension is one of the <u>more common late complications</u> seen in CREST syndrome
 - ⇒ The most common cause of death
- Malabsorption is most likely to develop as a further complication
 - ⇒ Involvement of GIT can occur from mouth to anus
 - can present with both diffuse and limited cutaneous forms.
 - Most GIT manifestations result from <u>dysmotility</u> secondary to <u>infiltration</u> of the intestinal wall with fibrous tissue,
 - can cause life-threatening malabsorption and malnutrition.
 - Gastric emptying is delayed in 10-75% of patients and causes symptoms of early satiety, bloating and emesis.
 - Treatments include metoclopramide and erythromycin.

- small bowel is also involved in 20-60% of patients, due to reduced or absent migrating motor complexes predisposing to bacterial overgrowth.
 - initial attempts at eradication of bacterial overgrowth with metronidazole, ciprofloxacin or co-amoxiclav is appropriate.
- The contributes to malabsorption, as does associated pancreatic insufficiency.
- In the colon there is often development of diverticuli involving all layers of the intestinal wall, or constipation due to reduced motility.

The limited symptoms of scleroderma are referred to as CREST



2. Diffuse cutaneous systemic sclerosis

- · less common.
- scleroderma affects trunk and proximal limbs predominately (although face may be involved in either type)
 - ⇒ Skin areas involved include also the upper arms, thighs or trunk.
- · associated with scl-70 antibodies
- hypertension, **lung fibrosis** and renal involvement seen
 - Pulmonary involvement is the second commonest organ involvement after oesophageal disease and is the leading cause of death.
 - ⇒ Pulmonary fibrosis is associated with anti-ScI-70 antibodies in up to 70% of cases
 - ⇒ scl-70 antibodies associated with a higher risk of severe interstitial lung disease
 - ⇒ Reduced DLCO is the earliest sign of pulmonary disease in systemic sclerosis, often before fibrotic changes manifest clinically.
- Diffuse cutaneous systemic sclerosis may lead to <u>scleroderma renal crisis (SRC)</u> in up to 10% cases.
 - ⇒ The underlying pathology of SRC is vasospasm.
 - ⇒ Features
 - SRC may present with rapid onset renal failure,
 - malignant hypertension,
 - micro-angiopathic haemolytic anaemia with schistocytes.
 - Patients may develop symptoms of fluid overload.
 - ⇒ Other risk factors for SRC include:
 - corticosteroid use (prednisolone more than 15 mg/day),
 - recent onset scleroderma (less than three years), and
 - involvement of other systems.
 - ⇒ Treatment involves starting ACE inhibitors.
- poor prognosis

3. Scleroderma (without internal organ involvement) tightening and fibrosis of skin may be manifest as plaques (morphoea) or linear







Antibodies

- ANA positive in 90%
 - ⇒ therefore, in a negative test → consider an alternative diagnosis
- RF positive in 30%
- Anti-centromere antibodies associated with limited cutaneous systemic sclerosis
- Anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
 - ⇒ (anti-Scl-70) also known as **Anti-topoisomerase I antibodies**
 - ⇒ associated with a higher risk of severe interstitial lung disease
- Anti-RNA polymerase III antibodies
 - ⇒ found in patients with diffuse disease
 - ⇒ associated with:
 - rapidly progressive skin involvement
 - increased risk for scleroderma renal crisis.
 - increased risk for cancer

Other investigations

Serum protein electrophoresis: ↑ γ-globulins

Treatment

- Immunosuppressive therapy: e.g., methotrexate
- Organ-specific therapy:
 - ➤ gastroesophageal reflux disease → PPIs
 - ➢ Renal crisis → ACE inhibitors
 - Renal crises result from an acute renal vasculopathy with associated hyperreninaemia, not glomerulonephritis.
 - ACE inhibitors in the acute setting improves long term survival, end organ damage due to hypertension, and can lead to an improvement in renal function even up to 2 years after crisis.
 - ⇒ Interstitial lung disease secondary to underlying diffuse systemic sclerosis:
 - The most appropriate treatment is cyclophosphamide
 - Azathioprine is normally used as maintenance therapy following cyclophosphamide.

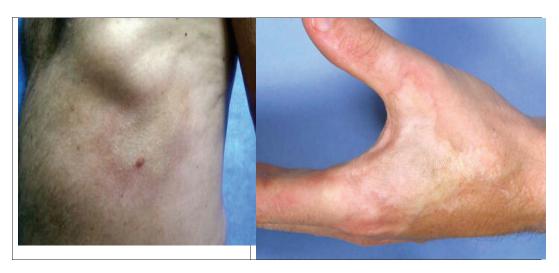
Prognosis

 U&Es have a crucial role with respect to determining prognosis and appropriate therapeutic intervention. the most important initial investigation with respect to determining patient outlook?
 → Urea and electrolytes

Sclerodema renal crisis

- A major complication of systemic sclerosis
- Severe and life threatening renal disease develops in approximately 10-15% of patients.
- Features
 - ⇒ severe hypertension, with diastolic BP over 100 mmHg, usually with grade III or IV hypertension retinopathy, together with rapid deterioration of renal function and heart failure:
 - ⇒ symptoms of malignant hypertension, with headaches, blurred vision, fits and heart failure.
 - ⇒ haematological tests often demonstrate a thrombocytopenia and/or microangiopathic haemolysis.
- Treatment
 - ⇒ Hypertension → ACE inhibitor (calcium channel blockers can be added).
 - While ACE inhibitors are generally avoided in most patients with acute renal failure, scleroderma renal crisis is an exception to the rule as long as renal function is closely monitored.
 - ⇒ Renal dialysis may be required.
 - ⇒ An excessive reduction in BP or hypovolemia (should be avoided) →
 ↓ renal perfusion → acute tubular necrosis. Thus, parenteral antihypertensive agents (such as intravenous nitroprusside or labetalol) should be avoided.

Morphea (localised scleroderma)



Definition

 idiopathic inflammatory skin condition which causes excessive collagen deposition and fibrosis.

Types

- Morphea is classified into subtypes according to the clinical presentation and depth of tissue involvement:
 - ⇒ circumscribed morphea,
 - the commonest form, "circumscribed/plaque" morphea.

- This is a well-defined oval to round plaque that fails to meet the criteria for generalised morphea.
- ⇒ generalized morphea,
- ⇒ pansclerotic morphea

Pathophysiology

- autoimmune component is suggested by enhanced T helper 2 (Th2) dependent interleukin 4 (IL-4) activity, which in turn upregulates transforming growth factor beta (TGF -beta).
- TGF-beta stimulates fibroblast production of collagen and other extracellular matrix proteins.

Features

- Unlike systemic sclerosis, morphea lacks features such as sclerodactyly, Raynaud phenomenon, nailfold capillary changes, telangiectasias, and progressive internal organ involvement.
- Morphea can present with extracutaneous manifestations, including fever, lymphadenopathy, arthralgias, fatigue, central nervous system involvement,

Investigations

- Hypergammaglobulinaemia (↑↑IgM , IgG)
- peripheral eosinophilia
- ↑↑ ESR and CRP
- Anti-Cu/Zn superoxide dismutase antibodies have been found in up to 90%

Treatment

- · Superficial circumscribed morphea
 - ⇒ Tacrolimus 0.1% ointment applied twice daily for 12 weeks may be a useful firstline
- Generalized, linear, or deep morphea
 - ⇒ combination therapy with oral prednisone and methotrexate
 - ⇒ To minimize the risk of relapse, the recommended treatment duration of MTX is at least 2 years.
 - ⇒ Systemic corticosteroids can be helpful in the inflammatory phases of morphea, but they are not recommended for long-term monotherapy
 - ⇒ Mycophenolate mofetil is a second-line

Prognosis

• generally resolves within 3–5 years, although sometimes a patch may persist for over 25 years.

Polymyalgia rheumatica (PMR)

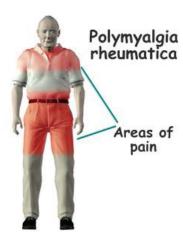
Pathophysiology

- overlaps with temporal arteritis 30% of patients also have giant cell arteritis.
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

Epidemiology

- occurring in patients age 50 years or older.
- More common in women

Features



- typically patient > 60 years old
 - ⇒ very rarely seen in the under 50s.
- usually rapid onset (e.g. < 1 month)
- typically presents with pain and stiffness of the shoulder and pelvic girdle muscles.
- aching, morning stiffness in proximal limb muscles (not weakness)
 - ⇒ Pain and muscle stiffness worst in the mornings
- mild polyarthralgia, lethargy,
- depression,
- low-grade fever, anorexia, night sweats
- Weight loss

Investigations

- ESR > 40 mm/hr
 - ⇒ the next best investigation
 - ⇒ a high ESR would prompt immediate treatment with steroids.
- Raised C reactive protein (CRP)
- Alkaline phosphatase is an acute-phase reactant and is raised in approximately a third of
 patients with polymyalgia rheumatica.
- note CK and EMG normal
- · reduced CD8+ T cells
- Normochromic / normocytic anaemia

Differential diagnosis

- Giant cell arteritis (GCA)
 - ⇒ GCA and PMR frequently co-exist,
 - cranial symptoms including headache, jaw claudication, and vision symptoms are typically absent in patients with PMR.
 - ⇒ PMR typically has less prominent symptoms than GCA.

Treatment

- prednisolone e.g. 15mg/od dramatic response
 - Response to a moderate dose of steroids can be useful in confirming the diagnosis of PMR.
 - ⇒ The maximum dose of prednisolone should not exceed 20 mg once daily.
 - ⇒ Patients should report 70% improvement in symptoms within three to four weeks, and inflammatory markers should have normalised by this point.

- ⇒ Calcium and vitamin D supplementation should be initiated for all patients with PMR who are starting corticosteroid therapy. Bisphosphonates should be added for long term steroid therapy.
- ⇒ The usual starting dose is 15 mg prednisolone per day.
- ⇒ Patients should expect relief of symptoms within 24-72 hours.
 - One of the best 'tests' for Polymyalgia Rheumatica (PMR) is how patients respond to corticosteroid therapy.
- ⇒ Tapering
 - Tapering should be guided by clinical response.
 - The dose should be increased if symptoms are not well controlled within one week.
 - The effective starting dose should be maintained for two to four weeks after the patient becomes asymptomatic.
 - Generally, the daily dose can be lowered by 1.0-2.5 mg every two to four weeks to find the minimum dose needed to maintain symptom suppression.
 Once the patient is reduced to 10 mg per day, the daily dose can be tapered by 1 mg every four weeks.
 - Approximately 50-75% of patients can discontinue corticosteroid therapy after two years of treatment.

⇒ Methotrexate and azathioprine

- If symptoms relapsed when the dose of prednisolone has been reduced below the current dose, → Continue the current dose of prednisolone and start methotrexate
- used in patients with corticosteroid intolerance or as corticosteroid-sparing agents.
- These are generally reserved for patients in whom it has been difficult to reduce the prednisolone after prolonged high dosages (for example, 10 mg or more per day for more than a year).
- These agents should be added to the prednisolone initially, but with a view to slowly reduce and withdraw prednisolone.
- As with steroid therapy, azathioprine or methotrexate can be discontinued if there has been sufficient response.

Prognosis

• Rapid improvement often occurs within 24 to 72 hours with low-dose prednisolone.

Temporal arteritis (Giant cell arteritis (GCA)

GCA should always be considered in elderly patients with headaches, ocular symptoms (e.g. acute monocular visual loss), systemic symptoms and high ESR.

Suspected GCA \rightarrow glucocorticoids <u>immediately</u>, even before diagnostic evaluation by temporal artery biopsy is complete.

Overview

- also known as giant cell arteritis (GCA).
- Temporal arteritis is large vessel vasculitis
- overlaps with polymyalgia rheumatica (PMR).
- Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.
- It is a clinical emergency.

Epidemiology

- Sex: ♀ > ♂
- Peak incidence: 70–79 years; rarely seen in patients < 50 years

Features

- typically, patient > 60 years old
 - ⇒ The greatest risk factor for (GCA) is aging.
 - ⇒ almost never occurs before age 50
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%) is a very specific sign for temporal arteritis.
- visual disturbances (50%)
 - ⇒ secondary to anterior ischemic optic neuropathy
 - ⇒ 15-20% of patients develop permanent visual loss.
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also, lethargy, depression, low-grade fever, anorexia, night sweats
- Large vessel GCA: Subclinical involvement of the aorta and large arteries is frequent, a clinical consequence of which can be <u>aortic aneurysm</u> (in 10 to 20 % of cases).

Investigations

- Raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
 - ⇒ ESR can be within normal range in 5-10% of GCA cases.
- Temporal artery biopsy:
 - ⇒ the definitive diagnostic test
 - skip lesions may be present (certain sections of affected artery whilst damaging others)
 - ⇒ An adequate length of temporal artery (3 to 5 cm) should be obtained because inflammatory lesions may be present in a segmental fashion.
 - ⇒ A negative temporal artery biopsy can occur in up to 50% of patients, often because
 the sampled region was not involved in the pathologic process. Therefore, it is not
 sensitive enough to rule out temporal arteritis.
 - ⇒ Treatment should not be delayed while waiting for the biopsy to be performed.
- Note: creatine kinase and EMG normal

Diagnosis

- The American College of Rheumatology 1990 criteria requires 3 of the following for GCA diagnosis:
 - 1. Age >50 y/o
 - 2. New onset localised headache
 - 3. Temporal artery tenderness or decreased pulsation
 - 4. ESR >50mm/hr
 - 5. Temporal artery biopsy positive

Treatment

- High-dose prednisolone
 - ⇒ there should be a dramatic response, if not the diagnosis should be reconsidered
 - **⇒** Current BSR guidelines recommend:
 - Uncomplicated GCA (no jaw or tongue claudication, or visual symptoms)
 prednisolone 40-60 mg daily
 - Complicated GCA: (with visual involvement and/or jaw/tongue claudication)

- Evolving visual loss or history of amaurosis fugax: IV methylprednisolone 500 mg-1 g daily for three days, followed by oral corticosteroids
- Established visual loss: at least 60 mg prednisolone daily
- · Urgent ophthalmology review.
 - Patients with visual symptoms should be seen the same-day by an ophthalmologist.
 - ⇒ Visual damage is often irreversible
- As GCA requires long-term steroid therapy bone sparing agents (a bisphosphonate and vitamin D) and a gastroprotective drug (e.g omeprazole) should be prescribed.
- Also, low dose aspirin should be considered as it has been shown to reduce the rate of visual loss and cerebrovascular accidents in GCA.

Polyarthritis

Differential diagnosis

- rheumatoid arthritis
- SLF
- seronegative spondyloarthropathies
- Henoch-Schonlein purpura
- sarcoidosis
- tuberculosis
- pseudogout
- viral infection: EBV, HIV, hepatitis, mumps, rubella

Polyarteritis nodosa (PAN)

Definition

- systemic vasculitis of the medium-sized vessels, with necrotizing inflammation leading to aneurysm formation and tissue ischemia;
- most commonly involving skin, peripheral nerves, muscles, joints, gastrointestinal tract, and kidneys.
- any organ with the exception of the lung can be affected,

Epidemiology

- Peak incidence: ~ 45-65 years
- Sex: ♂ > ♀
- more common in middle-aged men

Pathophysiology

- diffuse vascular inflammation and ischaemia of the affected organs.
- PAN is a medium-vessel vasculitis that is a type III hypersensitivity reaction.

Association

hepatitis B infection

Features

- Nonspecific symptoms: (found in 65% to 80% of patients)
 - ⇒ fever, malaise, arthralgia, weight loss
- Neurological involvement: (in 55% of patients)
 - ⇒ polyneuropathy (mononeuritis multiplex),
 - ⇒ cerebral ischemia (stroke)
- Skin involvement: (in 44%)
 - ⇒ skin rash,
 - ⇒ Skin ulcers, nodules
 - ⇒ livedo reticularis

- Renal involvement : (in 11%)
 - ⇒ hypertension,
 - Hypertension is a manifestation of <u>renal ischaemia via activation of the renin-</u> angiotensin system.
 - ⇒ haematuria
 - but red cell casts are absent because glomerular inflammation is not a feature.
 - ⇒ renal impairment
- Coronary artery involvement;
 - ⇒ increased risk of myocardial infarction
- Gl involvement:
 - ⇒ abdominal pain, nausea, vomiting
 - ⇒ can present with abdominal pain and melena due to involvement of the mesenteric arteries
- Testicular pain
 - ⇒ testicular pain from ischaemic orchitis is a characteristic feature
 - ⇒ uncommon presentation
- Usually spares the lungs

PAN should be considered in young adults presenting with stroke or myocardial infarction. The diagnosis may be confirmed with a biopsy of involved tissue



Livedo reticularis

Diagnosis

- The American College of Rheumatology (ACR) 1990 criteria
 - ⇒ Three of the following 10 criteria are required:
 - 1. Weight loss ≥4 kg
 - 2. Livedo reticularis
 - 3. Testicular pain or tenderness
 - 4. Myalgias, weakness, or leg tenderness
 - 5. Mononeuropathy or polyneuropathy
 - 6. Diastolic blood pressure >90 mmHg
 - 7. Elevated urea or creatinine
 - 8. Positivity for hepatitis B virus (HBV) infection
 - 9. Arteriographic abnormality

 Biopsy of small- or medium-sized artery containing polymorphonuclear leukocytes.

Investigations

- Hepatitis B surface antigen is positive in 30%,
- p-ANCA is positive **only** in 20%.
 - **⇒** ANCA is classically negative in PAN.
- Angiography:
 - Conventional angiography is <u>the imaging modality of choice</u>, and should be performed if there is a clinical suspicion of PAN.
 - ⇒ typically demonstrates:
 - microaneurvsms and
 - focal narrowing in medium-sized blood vessels.
- Biopsy
 - ⇒ should be performed <u>if angiography is not available or does not conclusively</u> show a medium-vessel vasculitis.
 - ⇒ Shows:
 - focal and segmental transmural necrotising inflammation with fibrinoid necrosis in medium-sized vessels.
 - pleomorphic cellular infiltrate of lymphocytes, neutrophils, macrophages, and eosinophils.
 - granulomas are absent.

Differential diagnosis

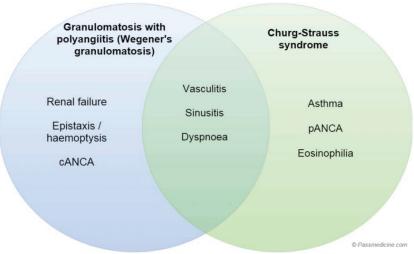
- PAN are differentiated from the other small- and medium-vessel vasculitides by:
 - ⇒ absence of anti-neutrophil cytoplasmic antibodies,
 - ➡ Glomerulonephritis is not a feature of PAN, but it is common in anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis. Making this distinction early by way of urinalysis for protein, blood, and <u>casts</u> is a <u>simple first-line test</u> that can guide further investigation and treatment.
 - Red cell casts are absent in PAN
 - If there is evidence of glomerular inflammation such as urinary casts, then an alternative diagnosis such as microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (Wegener's) (GPA),must be considered.
 - ⇒ lung involvement is not seen in PAN, and abnormal respiratory findings should suggest an alternative diagnosis
 - ⇒ and by confirmation that small vessels (i.e., arterioles, capillaries, venules) are not involved.

Treatment

- idiopathic PAN → corticosteroids and cyclophosphamide
- hepatitis B related disease → plasmapheresis and antiviral agents.
- Azathioprine can be used as maintenance therapy, and typically has fewer side effects than cyclophosphamide.

Cyclophosphamide \rightarrow causes premature ovarian failure and infertility in both men and women.

<u>Granulomatosis with polyangiitis (Wegener's granulomatosis)</u>



Overview

- Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis.
- It is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.
- · the classical triad consists of
 - 1. necrotising granulomatous inflammation of the respiratory tract,
 - 2. glomerulonephritis
 - 3. small-vessel vasculitis.

Features

- · upper respiratory tract: epistaxis, sinusitis, nasal crusting
- saddle-shape nose deformity
- lower respiratory tract: dyspnoea, haemoptysis
 - migrating alveolar shadowing
- rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
 - ⇒ It usually presents with rapidly progressing renal failure (within three months), proteinuria and microscopic haematuria.
- also:
 - ⇒ vasculitis (causing carotid artery tenderness)
 - ⇒ vasculitic rash,
 - ⇒ eye involvement (e.g. proptosis),
 - ⇒ cranial nerve lesions

Investigations

- c-ANCA (PR3-ANCA (targeting peroxidise-3) positive in > 90%, p-ANCA (MPO-ANCA (targeting myeloperoxidase) positive in 25%
 - ⇒ cANCA directed against proteinase-3
 - ⇒ cANCA is highly specific, but is **found in only 50% of patients with disease localised to the respiratory tract** and 95% with generalised Wegener's.

- In active Wegener's disease with renal involvement cANCA is highly sensitive and specific.
- After disease remission cANCA <u>may remain elevated for years</u>, and is <u>not useful in evaluating patients for relapse</u>.
- · chest x-ray: wide variety of presentations, including cavitating lesions
- tissue biopsy
 - ⇒ renal biopsy:
 - epithelial crescents in Bowman's capsule
 - Kidneys show vasculitis and glomerulonephritis and occasional (NOT always) granulomata
 - ⇒ Lung biopsy has a high diagnostic yield
 - show vasculitis and granulomas
 - ⇒ Biopsy of the upper respiratory tract shows granulomas but not vasculitis.

Management

- steroids
 - ⇒ **Prednisolone** is given in doses of around 1 mg/kg per day initially, after which the dose is reduced rapidly, typically at weekly intervals.
 - ⇒ In case of renal failure with indications for dialysis, the initial management →Methylprednisolone
 - Methylprednisolone should be given immediately, followed by haemodialysis and then cyclophosphamide.
- cyclophosphamide (90% response)
 - ⇒ The combination of prednisolone and cyclophosphamide is now established as the standard therapy and the treatment of choice for induction of remission in Wegener's granulomatosis
 - ⇒ Cyclophosphamide: Traditionally, oral dose (2 mg/kg per day), but latterly intravenous boluses have proved increasingly popular, given in doses of 0.5-0.75 g/m2 body surface area at intervals of 2 weeks (at least for short periods) to 2 months.
 - If a patient had a vasculitic neuropathy. Current practice is to use cyclophosphamide for induction therapy.
- Both rituximab and methotrexate have also been used for induction therapy in ANCA-associated vasculitis, although they would not be first-line treatment.
- Azathioprine is used as maintenance treatment following cyclophosphamide
- ciclosporin is rarely used in the management of ANCA-associated vasculitis.
- Evidence from controlled trials suggests that once remission is achieved azathioprine or methotrexate may be reasonable alternatives to cyclophosphamide.
- In refractory Wegener's, both infliximab and rituximab have shown some degree of promise.
- plasma exchange
- in case of <u>decreased conscious level</u> with acute renal failure (with indication for dialysis) and respiratory function is failing. The first immediate step → Endotracheal intubation and positive pressure ventilation, transfer the patient to a critical care setting (especially to protect airway with a GCS 8/15).

Prognosis

median survival = 8-9 years

Microscopic Polyangiitis

- PR3 antibody is associated with Wegener's granulomatosis,
- **▶** MPO antibody is associated with microscopic polyangiitis
- Microscopic polyangiitis is similar to wegener's granulomatosis except in 3 things:
 - 1. it only affects small blood vessels in the lungs or kidneys.
 - No nasopharyngeal damage like wegener's
 - 2. Associated with p-ANCA antibodies.
 - anti-MPO (pANCA, 45%) antibody is strongly positive than anti-PR3 (cANCA, 30%)
 - 3. No granuloma on biopsy

Microscopic polyangiitis is similar to Granulomatosis with polyangiitis (Wegener's granulomatosis) except in 3 things:

- 1. it only affects small blood vessels in the lungs or kidneys.(No nasopharyngeal damage like wegener's)
- 2. Associated more with anti-MPO (pANCA, 45%) than anti-PR3 (cANCA, 30%)
- 3. No granuloma on biopsy

PassOnExam

Churg-Strauss syndrome

- Churg-Strauss syndrome is an ANCA associated small-medium vessel vasculitis.
- also known as Eosinophilic granulomatosis with polyangiitis

Features

- asthma
- · paranasal sinusitis
- mononeuritis multiplex
- blood eosinophilia (e.g. > 10%)
- Serum IgE is very commonly elevated and correlates with disease severity.
- pANCA positive in 60%
- Commonly associated with antimyeloperoxidase antibodies.
- Non-fixed pulmonary infiltrates visible on chest radiographs
- Rarely, it can cause ischaemic optic neuropathy, which presents with visual loss.

Leukotriene receptor antagonists may precipitate the disease

Diagnosis

- It is diagnosed clinically, although a biopsy should be sought for pathological confirmation.
- Skin biopsy reveals small-vessel arteriopathy with granuloma formation and is the diagnostic investigation of choice.
 - ⇒ Blood vessels with **extravascular eosinophils** on biopsy.

Treatment

 High-dose methylprednisolone, with or without cyclophosphamide is the treatment of choice

Prognosis

• Without treatment, the 5-year survival rate for Churg-Strauss syndrome is around 25%; with appropriate therapy this rises to over 60%.

Idiopathic pulmonary haemosiderosis

- pulmonary hemorrhage <u>without immunological features</u> → Idiopathic pulmonary haemosiderosis
- **▶** pulmonary hemorrhage + immunological features → Goodpasture or wegener's

Definition

recurrent episodes of diffuse alveolar hemorrhage of unknown aetiology

Prevalence

- rare
- tends to occur in younger people

Features

- pallor,
- · weakness, lethargy,
- dry cough and occasional haemoptysis
- no extrapulmonary features.
- After recurrent episodes of hemorrhage, pulmonary fibrosis may develop due to iron accumulation.

Investigations

- no abnormal immunological features, which differentiates it from Goodpasture syndrome and wegener's
- Gas transfer is elevated as blood is already in the alveolar space.
- chest radiograph and high resolution computed tomography demonstrate ground glass alveolar opacities that are often bilateral.
- final diagnosis requires lung biopsy documentation of large numbers of hemosiderinladen macrophages in the alveoli, without evidence of vasculitis, capillaritis, inflammation, granulomas, or deposition of immunoglobulins in any specific pattern.

Treatment

 glucocorticoids +/- another immunosuppressive agent (eg, azathioprine, or cyclophosphamide)

Henoch-Schonlein purpura

Overview

- Henoch-Schonlein purpura (HSP) is an IgA mediated small vessel vasculitis
- involving mainly the blood vessels of the skin, GI tract, the kidneys and the joints.
- 90% of cases of HSP occur in children aged 2-10 years but can occur in any age group.
- In children, (HSP) is the most common cause of vasculitis affecting the kidneys.
- typically commoner in males,
- may follow an infectious agent.
- It can present one to three days following infection of an IgA secreting mucous membrane (commonly following pharyngitis, but can occur following infection of the gastrointestinal tract, bladder or breast).
- An important risk factor in adults → chronic alcohol intake.
- associated with: Helicobacter pylori, hepatitis B and malignancy.

Features

HSP is characterised by the **tetrad of**:

- purpura
- abdominal pain
- arthritis, and
- renal involvement (haematuria and proteinuria).
 - ⇒ Patients with proteinuria have a worse prognosis than patients with haematuria alone.
- palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs (due to a cutaneous vasculitis)
- abdominal pain (due to gut vasculitis, which may be severe in some cases, leading to bloody diarrhoea)
- polyarthritis (common symptom)
- features of IgA nephropathy may occur e.g. haematuria, renal failure
 - ⇒ HSP nephritis becomes clinically manifest in only 20-30%.
 - ⇒ It usually presents as macroscopic haematuria and proteinuria
 - ⇒ Of those patients with renal involvement, as many as 10% may develop chronic renal failure and end-stage renal disease. However, fewer than 1% of all patients with HSP suffer this poor prognosis.

Diagnosis

- Skin biopsy and immunofluorescence demonstrate leukocytoclastic vasculitis with IgA deposition, (meaning lots of white blood cells in the skin around small blood vessels) which is pathognomonic for HSP.
 - ⇒ Immunofluorescence studies will reveal → IgA deposits within blood vessel walls

Treatment

- analgesia for arthralgia
- treatment of nephropathy is generally supportive.
 - All patients with hypertension and proteinuria (greater than 1 g/day) should be started on an angiotensin-converting enzyme (ACE) inhibitor, which may control the BP and proteinuria.
 - Once the BP has been controlled, patient should have a renal biopsy, and if this showed changes of a crescentic glomerulonephritis (GN), then an immunosuppression regime similar to that used in renal vasculitis should be started (probably with high dose steroids in the first instance +/- cyclophosphamide).
 - ⇒ There is inconsistent evidence for the use of steroids and immunosuppressants
 - ⇒ Management of HSP in adults often involves the use of immunomodulatory or immune-suppressive regiments (in contrast to children where the majority of cases resolve spontaneously).

Prognosis

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- There is often a more complicated course in adults, and 50% of patients who present with renal involvement develop renal insufficiency.
- around 1/3rd of patients have a relapse

Henoch-Schonlein purpura (HSP) is the tetrad of:

- 1. Purpura
- 2. Abdominal pain
- 3. Renal involvement (haematuria and proteinuria)
- 4. Arthritis

Incidence: most common in children <17 years.

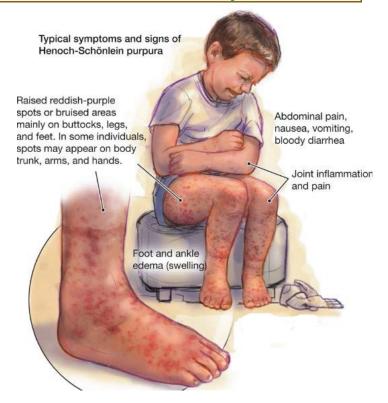
Mechanism: IgA mediated small vessel vasculitis.

Diagnosis: Skin biopsy → leukocytoclastic vasculitis with IgA deposits within blood vessel walls.

Treatment:

- For pain: 1st line → naproxen. 2nd line → prednisone.
- refor hypertension and proteinuria → ACE inhibitor.

Prognosis: self-limited → Full renal recovery.



MRCPUK-part-1-September 2019 exam: What is the most likely renal outcome in Henoch-Schonlein purpura? Full renal recovery

Kawasaki disease

Overview

- Kawasaki disease is a type of vasculitis which is predominately seen in children.
- Whilst Kawasaki disease is uncommon it is important to recognise as it may cause
 potentially serious complications, including coronary artery aneurysms

Features

- high-grade fever which lasts for > 5 days. Fever is characteristically resistant to antipyretics
- conjunctival injection
- · bright red, cracked lips
- strawberry tongue
- cervical lymphadenopathy
- red palms of the hands and the soles of the feet which later peel

Diagnosis

Kawasaki disease is a clinical diagnosis as there is no specific diagnostic test

Management

- high-dose aspirin
 - ⇒ Kawasaki disease is one of the few indications for the use of aspirin in children. Due to the risk of Reye's syndrome aspirin is normally contraindicated in children.
- intravenous immunoglobulin
 - Combination therapy with intravenous immunoglobulin (IVIG) and aspirin during the acute phase of Kawasaki disease produces a more marked antiinflammatory effect and reduction in coronary artery abnormalities than does aspirin alone.
- echocardiogram (rather than angiography) is used as the initial screening test for coronary artery aneurysms

Complications

- coronary artery aneurysm (25% of cases)
- lakayasu1s arter1 t1s

Kawasaki Disease

- Lymphomucocutaneous Disease
- Five Characteristics of Disease (4/5 for diagnosis)
 - Fever >5 days
 - Cervical lymphadenopathy (usually unilateral)
 - Erythema and edema of palms and soles with desquamation of skin
 - Nonpurulent Bilateral Conjunctivitis
 - Strawberry Tongue
- Treatment
 - IVIG and Aspirin

Takayasu's arteritis

Definition

- Chronic inflammatory granulomatous pan-arteritis of the major arteries
 - ⇒ It typically causes occlusion of the aorta (the ascending arch of the aorta)
 - The subclavian artery is commonly affected, and subclavian steal syndrome may occur
 - ⇒ The brachial, radial and ulnar arteries can also be involved.

Pathology

 continuous or patchy granulomatous inflammatory process involving macrophages, lymphocytes, and multinucleated giant cells which causes progressive occlusive disease of the aorta and its branches.

Epidemiology

- most commonly affects women (the ratio of women to men is 8:1).
- typical age onset of 25-30 years.
- most common in Asia.

Features

- questions commonly refer to an absent limb pulse.
- systemic features of a vasculitis e.g. malaise, headache
- unequal blood pressure in the upper limbs
- carotid bruit
- vascular symptoms such as claudication. (intermittent claudication)
- systemic symptoms of fever, arthralgia and weight loss.
- neurological symptoms such as transient ischaemic attacks.
- Cardiac features include angina, heart failure, and aortic regurgitation.
- Renal manifestations may include mesangial proliferative glomerulonephritis.
- aortic regurgitation (around 20%)
- ESR and CRP are usually elevated.
- levels of pentraxin 3 may be a useful marker of disease activity.

Associations

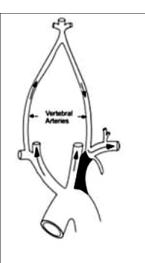
· renal artery stenosis

Treatment

 Corticosteroids with the addition of steroid sparing second agents such as methotrexate or azathioprine are the mainstay of therapy.

Prognosis

• With good care, 15-year survival rates approach 90%.



Subclavian steal syndrome (SSS)

The **proximal part of left subclavian is blocked on left side** so no flow in vertebral and to left arm. Blood from right vertebral enters left vertebral and flows back to supply left arm

Etiology

- Atherosclerosis
- Cervical rib
- Takayasu's arteritis

Features

- Presyncope (sensation that one is about to faint)
- Syncope (fainting)
- Neurologic deficits
- Blood pressure differential between the arms
- severe memory problems
- hands showing circulation problems (hands can have blotchy patches of red and white) (associated with other stigma to vascular disease (e.g. vascular insufficiency ulcers of the foot).

Buerger's disease

Overview

- Thromboangiitis obliterans (Buerger's disease) is a disease of small and medium-sized
 arteries and veins resulting in inflammation and ulceration, in which the distal vessels
 become blocked in the hands and feet.
- There is no excessive atheroma and it does not involve the coronary arteries like atherosclerosis.
- The disease occurs mainly in cigarette smokers; it has not been documented in nonsmokers.
- Although there is florid histological inflammation within vessels, the disease is not a
 systemic vasculitis, is not accompanied by any elevation in acute phase markers and does
 not respond to immune suppression.

Epidemiology

- Prevalence is higher in men and people of Far Eastern origin.
- seen in young (usually < 40 years) male smokers.

Feature

- symptoms of arterial ischaemia → resulting in gangrene of the digits.
 - ⇒ claudication with diminished or absent pulses.
 - ⇒ The feet or legs may be cyanosed or dusky; the skin is thin and without hair.
 - ⇒ Ulcerations occur, and necrosis follows
- Migratory phlebitis in the superficial vein is present in 40% of cases.

Diagnosis

- · usually clinical.
- Arteriogram will show occlusion of distal arteries of the hands and feet.
- Histopathology
 - examination of affected arteries reveals <u>fresh inflammatory thrombus</u> within both small and medium-sized arteries and veins, <u>with giant cells surrounding the</u> thrombus.

Treatment

- Supportive
- stop smoking.

Prognosis

- can be excellent (i.e. complete resolution of symptoms) with smoking cessation
- in some cases, however, amputation is unavoidable

IBD-associated arthropathy

- The history of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease (IBD).
- IBD-associated arthropathy is considered a subtype of seronegative spondyloarthropathy.
- A variety of joint involvement has been described, from large joint pauciarticular arthropathy to a rheumatoid pattern polyarthropathy.
- Peripheral arthritis is generally non-erosive and the oligoarticular variant particularly may correlate with intestinal disease activity.
- Axial arthritis may include inflammatory back pain, sacroilitis, or ankylosing spondylitis and is less likely to correlate with gastrointestinal symptoms.
- mechanisms remain unclear.
- Treatment of the gastrointestinal disease is not always sufficient for control of arthritis, and biologic agents may be indicated.

The description of weight loss, diarrhoea and a <u>mono/oligo-arthropathy</u> suggests a diagnosis of inflammatory bowel disease. (IBD).

Differential diagnoses of arthropathies associated with iron deposition in the joints →brown-stained synovial fluid.

- Haemophilia
- · Haemosiderosis from recurrent haemarthrosis
- · Haemochromatosis, and
- Pigmented villonodular synovitis (PVNS).

SAPHO syndrome

SAPHO is an acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis. It is characterised by osteosclerotic bone lesions, sterile osteomyelitis, and a variety of skin lesions.

- Synovitis may be present rarely, and associates with erosions.
- Acne may be severe (conglobate or fulminans) and recur with new bony involvement.
- Pustulosis palmo-plantar pustulosis occurs in approximately 50% of patients, other skin lesions may include psoriasis, hidradenitis suppurativa, acne, and rarely Sweet's syndrome.
- Hyperostosis (increase in bone substance) and osteitis (inflammation of the bones) the
 bony lesions typically involve the acromioclavicular, and sternoclavicular joints. Other sites
 include anterior chest wall, sternum, clavicle, pubic symphysis, spine, and mandible. These
 lesions are visualised on 99m technetium bone scan or MRI.

The cause of the SAPHO syndrome is unknown.

Investigation

- skin lesions are characterised by neutrophilic pseudoabscesses.
- Bone biopsy can reveal sterile osteomyelitis.

Diagnosis should be suspected when there is an association of rheumatic pain with a pustular skin disease.

treatment

- no specific treatment,
- some cases remit spontaneously

- Typical treatment can be used for the arthritic symptoms (i.e. non-steroidal antiinflammatories and disease modifying anti-rheumatic agents).
- Isotretinoin and aciretin can be used to treat the skin disease.
- In the more severe cases corticosteroids, calcitonin, bisphosphonates and TNF-inhibitors can be used.

Elbow pain

The table below details some of the characteristic features of conditions causing elbow

pain:			
Lateral epicondylitis (tennis elbow)	Features • pain and tenderness localised to the lateral epicondyle • pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended • episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks • most appropriate to gain short term relief for the patient? → Local steroid/anaesthetic injection		
Medial epicondylitis (golfer's elbow)	Peatures pain and tenderness localised to the medial epicondyle pain is aggravated by wrist flexion and pronation symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement		
Radial tunnel syndrome	Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse. Features symptoms are similar to lateral epicondylitis making it difficult to diagnose however, the pain tends to be around 4-5 cm distal to the lateral epicondyle symptoms may be worsened by extending the elbow and pronating the forearm		
Cubital tunnel syndrome	Due to the compression of the ulnar nerve. Features initially intermittent tingling in the 4th and 5th finger may be worse when the elbow is resting on a firm surface or flexed for extended periods later numbness in the 4th and 5th finger with associated weakness		
Olecranon bursitis	Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients.		

Shoulder problems

The table below summarises the key features of common shoulder problems:

Condition	Notes
Adhesive capsulitis (frozen shoulder)	Common in middle-age and diabetics Characterised by painful, stiff movement Limited movement in all directions, with loss of external rotation and abduction in about 50% of patients
Supraspinatus tendonitis (Subacromial impingement, painful arc)	Rotator cuff injury Painful arc of abduction between 60 and 120 degrees Tenderness over anterior acromion

Prepatellar bursitis

■ The most useful in initial diagnosis of prepatellar bursitis → Crepitation of the knee

Polymyositis

Polymyositis is the commonest cause of inflammatory muscle disease in people under 50-years-old (inclusion body myositis is the commonest in those over 50-years-old).

Anti-Jo-1 antibodies are more common in polymyositis than dermatomyositis

Definition

• Inflammatory disorder causing **symmetrical**, **proximal**, **painless** muscle weakness

Pathophysiology

thought to be a T-cell mediated cytotoxic process directed against muscle fibres

Epidemiology

- · Typically affects middle-aged
- Female: male 3:1

Associated conditions

- · Connective tissue disorders
- Interstitial lung disease → evaluate with chest x-ray and pulmonary function tests.
- Malignancy, commonly Adenocarcinomas, stronger for dermatomyositis, than for polymyositis. The most appropriate next investigation → CT chest, abdomen and pelvis

Features

- Proximal muscle weakness +/- tenderness
- Raynaud's
- Mechanics hands found in a subtype of polymyositis called anti-synthetase syndrome or Jo-1 syndrome →fissuring and cracking on the distal digital pads of several fingers.
- Respiratory muscle weakness
- Interstitial lung disease: e.g. fibrosing alveolitis or organising pneumonia
- Dysphagia, dysphonia

Investigations

- Elevated creatine kinase (the initial investigation)
- Electromyography (EMG): abnormal in almost all patients (90%).
 - ⇒ Triad of:
 - 1. Short, small polyphasia motor units
 - 2. Fibrillation and sharp waves
 - 3. Bizarre, repetitive discharges
- Muscle biopsy
 - ⇒ the definitive investigation to establish the diagnosis
 - ⇒ Histopathology → endomysial mononuclear inflammatory infiltrate with CD8 T cells (MHC class I) and muscle fiber necrosis.
- Anti-Jo-1 antibodies
 - ⇒ seen in pattern of disease associated with lung involvement, Raynaud's and fever
- Antinuclear antibody Positive in one third

Treatment

- Prednisolone is the mainstay of treatment, at an initial dose of 1 mg/kg/d.
- In patients who fail to show improvement, disease-modifying steroid-sparing agents may be added.
- A high-protein diet and supervised exercise may further improve symptoms.

Prognosis

 Most patients have a favourable response to corticosteroid therapy, and 5-year survival rates approach 80%.

Dermatomyositis

Proximal weakness with normal reflexes and sensation and absence of fasciculations:

- **⇒** without skin lesion → polymyositis
- **②** with skin lesion → dermatomyositis

Dermatomyositis antibodies: ANA most common, anti-Mi-2 most specific

Definition

Dermatomyositis is a variant of an inflammatory myositis causing symmetrical, proximal
muscle weakness and characteristic skin lesions, for example a purple Heliotrope rash on
the cheeks and eyelids or Gottron's papules: roughened red papules over extensor
surfaces of fingers

Pathophysiology

- Autoantibodies binding to the vasculature, muscle atrophy, and lymphocytic inflammation
- caused by <u>CD4</u> T cells that cause perimysial inflammation and atrophy.

Features

- **Features of polymyositis** (proximal muscle weakness, Raynaud's, respiratory muscle weakness, interstitial lung disease, dysphagia, dysphonia)
- Pathognomonic skin features
 - ⇒ **Heliotrope rash** in the periorbital region
 - a violaceous or erythematous rash in a symmetrical distribution involving periorbital skin.
 - its presence is highly suggestive of dermatomyositis .
 - ⇒ **Gottron's papules**: roughened red papules over extensor surfaces of fingers
- Other skin lesions
 - ⇒ Photodistributed erythema, poikiloderma, nailfold changes
 - ⇒ Mechanic's hands: (rough, cracked skin)
 - ⇒ Fingers telangiectasia: Nail fold capillary dilatation.
 - ⇒ Shawl sign: macular rash over back and shoulder
 - ⇒ **V-neck sig**: Violaceous erythema or poikiloderma involving the anterior chest
- ↑↑↑ risk of malignancy

Associated features

- Malignancies (dermatomycotic increases the risk of malignancy more than polymyositis). typically lung cancer, found in 20-25%
- Interstitial lung disease (ILD) occurs in at least 10%



Image shows: Heliotrope rash

Investigations

- Elevated creatine kinase → the most helpful initial test
- EMG
- Muscle biopsy
 - ⇒ high levels of the complement component C5b-9 around the capillary vessels.
 - ⇒ Perimysial inflammation with lymphocytic infiltrate
 - ANA positive in 60%

- Anti-Mi-2 antibodies are highly specific for dermatomyositis, but are only seen in around 25% of patients
- Screen for malignancy

Management

- Prednisolone
- Glucocorticoid-sparing agents: azathioprine or methotrexate.

Prognosis

Relatively good, with most patients reaching remission after 2–3 years, except of course
where there is an associated underlying malignancy.

Inclusion body myositis (IBM)

Definition

- a syndrome of diffuse, progressive, <u>asymmetric</u>, proximal, and distal weakness that is generally <u>refractory to immunosuppressive treatment</u>.
- The aetiology of IBM is largely unknown.

Epidemiology

- IBM occurs more frequently in men than women.
- More common in older Caucasian males.
- the most common acquired myopathy in patients older than 50 years

Features

- Muscle weakness can affect both proximal and distal muscles
 - ⇒ unlike polymyositis and dermatomyositis, asymmetry is common.
 - characteristically early affects quadriceps and finger/wrist flexors are usually more severely
 - ⇒ The onset of muscle weakness in IBM is generally gradual (over months or years).
- Dysphagia is common, occurring in 40-66% of patients
- Difficulties with breathing →the most common cause of death is respiratory system disorders.

Diagnosis

- creatine kinase (CK) levels: no striking elevation (less than 10 times normal)
- anti-cN1A autoantibodies
- Muscle biopsy
 - ⇒ shows intranuclear or cytoplasmic tubofilaments on electron microscopy.
 - ⇒ The specific finding is the presence of sarcoplasmic "rimmed" vacuoles

Treatment

- Optimal treatment for IBM is not known
- In contrast to dermatomyositis and polymyositis, IBM is relatively resistant to standard immunomodulatory therapies.

	Polymyositis	Dermatomyositis	IBM	
Onset	Subacute	Subacute	Slow	
age	Commonest < 50 years	Commonest < 50 years	commonest > 50 years	
Affected muscles	Proximal	Proximal Proximal and distal		
symmetry	symmetrical	symmetrical	Asymmetrical	
Common incidence	Female	Female	Male	
Skin lesion	NO	Characteristic rash	NO	
СК	Highly elevated (up to 50 fold)	Highly elevated (up to 50 fold)	Mild elevated (up to 10 fold) or normal	
antibodies	anti-Jo-1 are more common	anti-Mi-2 are highly specific	anti-cN1A autoantibodies	
Muscle biopsy	endomysial mononuclear inflammatory infiltrate and muscle fiber necrosis.	perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration/regeneration	intranuclear or cytoplasmic tubofilaments	
T cell	CD8 T cell	CD4 T cell		
Response to steroids	good	Good	Poor	

Painless weakness and wasting with selective involvement of long finger flexors and quadriceps is characteristic of inclusion body myositis.

Inclusion body myositis occurs in older people, has an insidious onset, and does not associate with striking elevations in CK.

Fibromyalgia (FM)

Definition

• Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites.

Epidemiology

- Prevalence: occur in 1 2% of the general population
- Gender: women are 10 times more likely to be affected
- Age: typically presents between 30-50 years old

Features

- · general symptoms: lethargy
- musculoskeletal symptoms:
 - ⇒ chronic pain: at multiple site, sometimes 'pain all over'
 - ⇒ allodynia: (pain in response to non-painful stimuli)
 - ⇒ Morning fatigue

 - ⇒ tissue swelling,
- neurological and psychiatric symptoms:
 - ⇒ sleep disturbance, headaches, dizziness are common
 - ⇒ patients often look unwell and may appear depressed and anxious.
- GIT symptoms:
 - ⇒ 50% of patients with fibromyalgia complain of **diarrhoea and constipation**, often associated with abdominal bloating.

Diagnosis

- The diagnosis of FM should be considered in any patient with >three months of widespread, multisite pain without apparent causative found.
- is clinical → pain in all four quadrants of the body, as well as tenderness in 11 of 18 anatomically defined trigger areas.
- The <u>normal ESR</u> in patients with FM contrasts with the high ESR in elderly patients with polymyalgia rheumatica.
- Other causes of fatigue should be excluded e.g. hypothyroidism, anaemia and other rheumatological diseases

Management

- explanation
- · aerobic exercise: has the strongest evidence base
- cognitive behavioural therapy
- · medication: pregabalin, duloxetine, amitriptyline

Key facts:

- How to diagnose?
 - A female, presented with a feature of pain and tenderness over multiple area + normal ESR and CRP.
- What is the best management?
 - ⇒ aerobic exercise

Dupuytren's contracture

Definition

- progressive painless contracture of the palmar facial bands, causing flexion deformities of the fingers.
- autosomal-dominant condition with variable penetrance.

Prevalence

- has a male: female predominance of 10:1.
- prevalence rates approaching 25% in elderly Scandinavians.
- most commonly observed in persons of Northern European descent and affects 4-6% of Caucasians worldwide.

Pathophysiology

- fibroblast proliferation, and collagen deposition leading to contractures of the palmar fascia.
- Interleukin 1 (IL-1) is the most abundant cytokine
- Normal palmar fascia is primarily composed of type I collagen; Dupuytren disease is associated with an increase in type III collagen.

Risk factor

- **Alcoholism** (10%),
- diabetes mellitus (8%).
- · previous myocardial infarction,
- hand trauma,
- HIV infection.
- cigarette smoking.

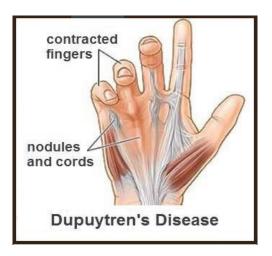
Features

- bilateral in 45%;
- in unilateral cases, the right side is more often affected.
- The ring finger is most commonly involved, followed by the fifth digit and then the middle finger. The index finger and the thumb are typically spared.
- Penile fibromatosis (Peyronie's disease) is seen in about 7-10% of patients.

Rheumatoid arthritis seems to protect against the development of Dupuytren disease.

Management

- Surgery followed by physiotherapy to improve finger function is the recommended course of action.
- Collagenase therapy may be an alternative to surgery in some cases.



<u>Ledderhose disease</u> is involvement of the plantar fascia by a similar process of nodule and cord formation leading to **contraction of the toes**.

Baker cyst

Look for a patient with osteoarthritis or rheumatoid arthritis with a swollen calf. A ruptured Baker's cyst is a "pseudophlebitis." Unruptured cysts can be palpated.

Overview

- A Baker's cyst (popliteal cyst) is a posterior herniation of the synovium of the knee.
- A Baker cyst is the most common mass in the popliteal fossa.
- Since the cyst is an extension from the knee joint, it is lined by synovium.

Causes

the most common cause → osteoarthritis

Investigations

 Ultrasonography is the imaging technique of choice in the evaluation of a popliteal mass, but using this technique it may be difficult to show a true connection with the joint space to establish a definitive diagnosis of popliteal cyst.

Third edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Infectious diseases

Updated 2022

Classification of bacteria

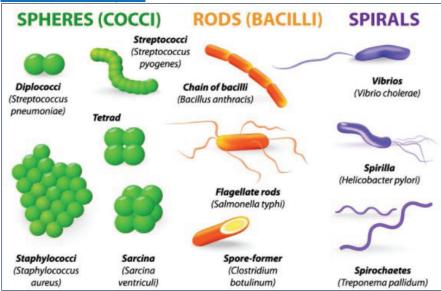
cocci

- Remember:
 - ⇒ Gram positive cocci = staphylococci + streptococci (including enterococci)
 - ⇒ Gram negative cocci = Neisseria meningitidis + Neisseria gonorrhoeae, also Moraxella

Rods (bacilli)

- only a small list of <u>Gram positive rods</u> (bacilli) need to be memorised to categorise all bacteria - mnemonic = ABCD L
 - ⇒ Actinomyces
 - ⇒ Bacillus anthracis (anthrax)
 - ⇒ Clostridium
 - ⇒ **D**iphtheria: *Corynebacterium diphtheria*
 - ⇒ **L**isteria monocytogenes
- Remaining organisms are Gram negative rods

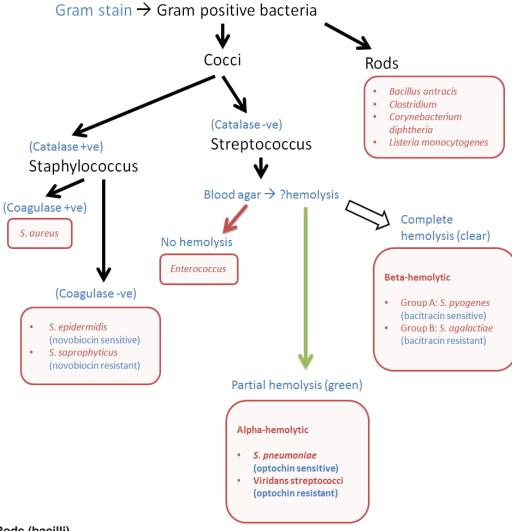
Bacterial shapes



 Staphylococcus aureus appears as large Gram-positive cocci in clusters.

Identifying gram-positive bacteria

Gram positive bacteria will turn purple/blue following the gram staining. Microscopy will then reveal the shape, either cocci or rods.



Rods (bacilli)

- Actinomyces
- Bacillus antracis
- Clostridium
- Corynebacterium diphtheriae
- Listeria monocytogenes

Cocci

- makes catalase: Staphylococci
- does not make catalase: Streptococci

Staphylococci

- makes coagulase: S. aureus
- does not make coagulase: S. epidermidis (novobiocin sensitive), S. saprophyticus (novobiocin resistant)

Streptococci

- partial haemolysis (green colour on blood agar): α-haemolytic
 - ⇒ optochin sensitive: S. pneumoniae
 - ⇒ optochin resistant: Viridans streptococci
- complete haemolysis (clear): β-haemolytic
 - ⇒ bacitracin sensitive: Group A: S. pyogenes
 - ⇒ bacitracin resistant: Group B: S. agalactiae
- no haemolysis: γ-haemolytic

Staphylococci

Most common organism found in central line infections - *Staphylococcus* epidermidis

Staph aureus is a coagulase positive Staph

- Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease.
- Staphylococci are skin organisms most commonly introduced during pacemaker insertion and such a discitis would present with back pain.

Basic facts:

- · Gram-positive cocci
- · facultative anaerobes
- produce catalase

Coagulase test:

- used to differentiate between different Staphylococcus species
 - Coagulase-Positive Staph species:
 - Staph aureus is the most important of the coagulase positive Staphylococcus species and is highly pathogenic.
 - Coagulase-negative Staph species:
 - most likely to be skin commensal organisms of relatively low pathogenicity, such as Staph epidermidis or Staph saprophyticus, although some may still cause deeper infection or sepsis.

Types

• The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

Staphylococcus aureus	Staphylococcus epidermidis
Coagulase-positive Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome	Coagulase-negative Cause of central line infections and infective endocarditis

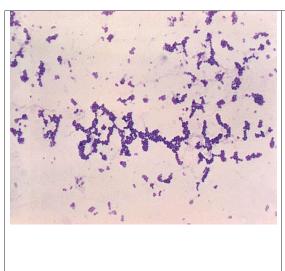
- Nasal swabs should be routinely checked in patients with recurrent staphylococcal abscesses
- Recurrent skin infections caused by staphylococcus often reflect colonisation that will
 require use of clearance procedures (body wash and topical nasal treatment) in order to
 prevent ongoing recurrences.
- This is particularly important in younger <u>athletes</u> in whom colonisation with resistant staphylococcal strains can occur.

Staphylococcus aureus

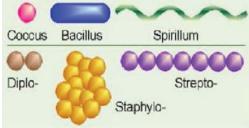
- catalase and coagulase positive, beta hemolytic organism.
- produces a <u>yellow</u> pigment ('Aureus' is Latin for 'gold'.)
- stained <u>purple</u> by gram staining.
- Staphylococcus aureus produce exotoxins that lead to three syndromes:
 - 1. food poisoning, caused by ingestion of S. aureus enterotoxin;
 - S. aureus is the most common cause of food poisoning.
 - The <u>enterotoxin</u> produced by Staphylococcus aureus (heat <u>stable</u> toxin) causes rapid-onset food poisoning.
 - Staph bacteria are killed by cooking, but the toxins are not destroyed
 - 2. scalded skin syndrome, caused by exfoliative toxin; (Exfoliatin A and B)
 - 3. toxic shock syndrome (TSS), caused by toxic shock syndrome toxin-1 (TSST-1)
- What is the mechanism by which methicillin-resistant Staphylococcus aureus gains resistance to penicillins?
 - > Alterations in penicillin-binding proteins

Effective antibiotics:

- Staphylococcal and streptococcal organisms are effectively treated by semisynthetic penicillins, including oxacillin, nafcillin, dicloxacillin, and cloxacillin. Also, first- and second-generation cephalosporin
- Penicillin G, ampicillin, and amoxicillin: These agents are effective against streptococci, such as S. pyogenes, viridans group streptococci, and S. pneumonia, but not against staphylococci
- Ampicillin and amoxicillin are only effective against staph when ampicillin is combined with the beta-lactamase inhibitor sulbactam or when amoxicillin is combined with clavulanate.



- The Gram stain shows Gram positive cocci growing in clusters, typical of Staphylococcus aureus.
- This is the most likely organism to cause post-operative infection of prosthetic joints within the first one to four weeks following surgery.



Streptococci

- Streptococci are gram-positive cocci.
- · divided into alpha and beta haemolytic types

Alpha haemolytic streptococci (partial haemolysis)

- The most important alpha haemolytic Streptococcus is Streptococcus pneumoniae (pneumococcus).
 - ⇒ carried asymptomatically in approximately 50% of people.
 - ⇒ It can cause both non-invasive and invasive disease.
 - Non-invasive:
 - includes otitis media, sinusitis, pneumonia and bronchitis.
 - Invasive pneumococcal disease (IPD)
 - refers to disease in which the bacterium enters a sterile site such as blood, cerebrospinal fluid, pleural fluid or pericardial fluid.
 - ⇒ If grow in blood cultures → IPD by definition.
 - more common in HIV-infected patients (20-30 times) compared to non-HIV infected patients.
 - ⇒ offer HIV testing to all patients with IPD presenting to hospital.
 - Other immunodeficiency syndromes are associated with an increased risk of IPD, include:
 - ⇒ X-linked (Bruton's) agammaglobulinaemia,
 - ⇒ common variable immunodeficiency,
 - ⇒ asplenia (anatomical or functional) and sickle cell disease.
 - ⇒ the mechanism of resistance for penicillin resistant Streptococcus pneumoniae
 → Alteration of penicillin binding proteins (PBPs)
 - Penicillin is a bactericidal antibiotic which acts by inhibiting cell wall synthesis.
 - Mutations in PBPs (enzymes required for cell wall synthesis) result in penicillin resistance.
- Another clinical example is Streptococcus viridans

Beta haemolytic streptococci (complete haemolysis)

These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

Group A

- ⇒ most important organism is *Streptococcus pyogenes*
- ⇒ responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis
- ⇒ immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis
- ⇒ erythrogenic toxins cause scarlet fever
- ⇒ Penicillin is the antibiotic of choice for group A streptococcal infections. The BNF suggests stopping flucloxacillin if streptococcal infection is confirmed in patients with cellulitis, due to the high sensitivity.

Group B

- ⇒ Streptococcus (GBS) agalactiae
 - Maternal vaginal colonization with GBS, primarily Streptococcus agalactiae, is associated with serious and highly fatal neonatal infections, such as sepsis and meningitis.
 - Lipoteichoic acid is the primary virulence factor of this organism
 - A prerequisite to mucosal colonization or infection is bacterial adherence to the epithelium. Lipoteichoic acid, a cell wall glycolipid polymer, mediates attachment of GBS to the vaginal epithelial cells. Lipoteichoic acid is also involved in host cell adherence of other Gram-positive bacteria as well. Without this adhesion, it would not be possible to have infection.

Group D

⇒ Enterococcus

Bacteria and growing media

Bacteria	Туре	Growth media
Staphylococci	Gram-positive cocci in clusters	LB broth agar
Streptococcal species (hemolytic Streptococcal species such as Streptococcus pyogenes).	Gram-positive cocci in chains	Trypticase Soy Agar (TSA) supplemented with 5% Sheep Blood
Streptococcus pneumoniae	Gram-positive bullet- shaped diplococci	Todd Hewitt Broth
E. coli, Klebsiella, or Enterobacter.	Gram-negative lactose fermenting bacilli	Super Optimal Broth (SOB)
Neisseria meningitidis	gram-negative diplococcus	chocolate agar

Enterococcus

Classification

- Previously classified as group D streptococci
- In the 1980s, based on genetic differences, enterococci were removed from the genus Streptococcus and placed in their own genus, Enterococcus

Enterococcus species

- E. faecalis: the predominant enterococcal species, 80 to 90% of all clinical isolates,
- E. faecium: 5 to 15%
- Others: (E. gallinarum, E. casseliflavus, E. durans, E. avium, and E. raffinosis) less than 5%

Importance

- Enterococci are currently ascendant nosocomial (عدوى المستشفيات) pathogens, due to their intrinsic resistance to several commonly used antibiotics
 - ⇒ the second most common organisms recovered from nosocomial urinary tract and wound infections
 - ⇒ the third most common cause of nosocomial bacteremia in the United States

Treatment

- Until recently, **vancomycin** was virtually the only drug that could be consistently relied on for the treatment of infections caused by <u>multidrug-resistant enterococci.</u>
 - ⇒ Oral vancomycin, which is poorly absorbed, has been used extensively for the treatment of Clostridium difficile enterocolitis.
- Teicoplanin is another glycopeptide antibiotic; Because of their activity against methicillinresistant staphylococci and other gram-positive bacteria, these drugs have been widely used for therapy and prophylaxis against infections due to these organisms

Vancomycin-resistant enterococci

- Risk Factors
 - ⇒ patients in ICUs
 - ⇒ prolonged hospitalization
 - ⇒ patients with chronic renal failure, cancer, or organ transplant recipients,
 - ⇒ Vancomycin use has been reported consistently as a risk factor for colonization and infection with VRE and may increase the possibility of the emergence of vancomycin-resistant S. aureus or S. epidermidis.
- Modes of Transmission
 - ⇒ Transmission of VRE by health care workers whose hands become transiently contaminated with the organism while caring for affected patients is probably the most common mode of nosocomial transmission.
- Clinical problems
 - ⇒ When they cause clinical problems, they are usually urinary tract infections (UTI), bacteraemia, wound infections, neonatal infections, endocarditis, etc.
- Sources
 - ⇒ May be found in healthy community volunteers not recently hospitalised
 - ⇒ Community reservoir in meat, poultry and perhaps cheese.
- Mechanism of resistance
 - ⇒ Vancomycin-resistant enterococci alter peptidoglycan precursors used to build cell walls. Vancomycin binds to D-ala-D-ala but the resistant enterococci have D-ala-D-lac or D-ala terminating precursors.
 - ⇒ They acquire genes that produce enzymes to change the precursors.

Anthrax

Overview

- Anthrax is caused by Bacillus anthracis, a Gram-positive rod. aerobic, non-motile
- It is spread by infected carcasses
- It produces serious disease in the herbivore host and carnivores acquire the disease from either consuming the spores from the dead animal or by contact.
- It is also known as Wool-sorters' disease.
- Cutaneous disease is the commonest form of the infection in humans and is usually due to contact with infected animals or animal products.

Toxins

- Bacillus anthracis produces a tripartite (composed of 3 parts) protein toxin
 - 1. protective antigen
 - oedema factor: a bacterial adenylate cyclase which increases cAMP
 - 3. lethal factor: toxic to macrophages

Features

- painless non-tender black eschar (cutaneous 'malignant pustule', but no pus)
 - ⇒ Following exposure, the skin lesion evolves over a period of ~2 weeks into a papule, pustule, vesicle and eventually forms an ulcer with a central black eschar.
 - ⇒ The surrounding skin is usually boggy and oedematous.
 - ⇒ Lesions are usually painless with tender regional lymph nodes.
- may cause marked oedema
 - ⇒ Edema factor toxin from *Bacillus anthracis* acts to mimic adenylate cyclase, thus <u>increasing</u> cAMP levels.
- anthrax can cause gastrointestinal bleeding

Investigations

 Inhalational anthrax is associated with a poor yield from sputum culture with the greatest yield from blood culture.

Management

- Lesions heal spontaneously in 80-90% of cases;
- 10-20% of patients progress and become bacteraemic associated with a high mortality.
- Penicillin is effective in treating the infection.
- the current Health Protection Agency advice for the initial management of cutaneous anthrax is ciprofloxacin
- further treatment is based on microbiological investigations and expert advice

Prognosis

 Mortality from cutaneous disease is 20% if untreated whereas inhalational anthrax may have a mortality of 90% if untreated.



Cutaneous anthrax

Diphtheria

Overview

- · caused by Corynebacterium diphtheriae,
- Corynebacterium diphtheriae is a **Gram positive**, non-spore-forming, pleomorphic bacteria that is also a facultative anaerobe.
- There are three recognised strains of *C.diphtheria*: gravis, intermedius, and mitis.
 - ⇒ Intermedius is thought to be the one most associated with the exotoxin and is more virulent than the mitis strain.
- Incubation period: 2 5 days,
- patients may be infectious for 4 weeks.
- Diphtheria is spread by droplets, through contact with soiled articles (fomites), and, in areas
 of poor hygiene, from cutaneous spread.

Pathophysiology

- The inflammatory exudate forms a greyish membrane on the tonsils and respiratory tract which may cause respiratory obstruction.
- Diphtheria toxin inhibits elogation factor (EF-2)
- Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Attempts to remove the pseudomembrane result in bleeding. Systemic distribution may produce necrosis of myocardial, neural and renal tissue.
- Exotoxins produced by the organism may cause myocarditis or neurological defects.
- secretion of an exotoxin that interferes with cellular protein synthesis, resulting in tissue necrosis.
- The exotoxin is composed of two chains:
 - 1. **chain B** is responsible for entry into host cells,
 - 2. **chain A** inhibits protein synthesis and causes cell death

Feature

history of severe exudative pharyngitis in a person who has recently travelled to eastern Europe is highly suggestive of diphtheria.

- Typically, diphtheria attacks the respiratory system, but may also affect the skin, conjunctiva, and external genitalia.
 - Cutaneous diphtheria presents with non-healing ulcers covered with a grey membrane, which can develop bacterial co-infection.
 - If isolated, the disease is indolent, but the ulcers can act as a reservoir which can subsequently lead to pharyngeal infection.
- Pharyngeal diphtheria presents with:
 - ⇒ fever
 - ⇒ sore throat
 - ⇒ cervical lymphadenopathy,
 - 'bulls neck' which results from cervical lymphadenopathy and mucosal swelling.
 - ⇒ adherent, grayish pharyngeal membrane.

- Neurological: cranial neuropathies, predominantly motor peripheral neuropathy (occasionally sensory neuropathy).
- Cardiac involvement is usually in the form of a cardiomyopathy and myositis, which is evident from the 10-14th day and may lead to arrhythmias. This accounts for 50% of deaths

Treatment

- isolation, securing a definitive airway, cardiac monitoring,
- antibiotic therapy and diphtheria antitoxin.
 - ⇒ benzylpenicillin: children: 2.4 to 4.8 g/day intravenously/intramuscularly given in divided doses every 6 hours for 14 days
 - ⇒ OR procaine benzylpenicillin 600,000 units intramuscularly once daily for 14 days
 - ⇒ OR Erythromycin 250-500 mg orally four times daily for 14 days
- Early administration of antitoxin is necessary to enable it to bind to and de-activate the free
 toxin in serum. Antitoxin cannot de-activate toxin once it has entered cells, which is
 signalled by the presence of mucocutaneous symptoms.
- Patients with respiratory diphtheria are placed in respiratory isolation (masks and standard measures such as hand-washing), and those with cutaneous diphtheria are placed in contact isolation (gloves and gowns), until cultures taken after cessation of therapy are negative.
- · close contacts of respiratory and cutaneous cases:
 - ⇒ cultures taken immediately
 - ⇒ prophylactic antibiotic (Erythromycin 250 mg orally four times daily for 7-10 days **Or** benzathine benzylpenicillin 1.2 million units intramuscularly as a single dose.
 - ⇒ diphtheria toxoid immunisation

Complications

• The toxin affects the myocardium, nervous and adrenal tissues.

Listeria

Listeria meningitis should always be considered in patients with meningitis associated with brain stem involvement, in elderly and in immunosuppressed patients. The treatment of choice is gentamicin and ampicillin.

- Listeria monocytogenes is a Gram positive bacillus
- has the unusual ability to multiply at low temperatures.
- It is typically spread via contaminated food, typically unpasteurised dairy products.
- infection is particularly dangerous to the unborn child where it can lead to miscarriage.
- Listeriosis is associated with the consumption of soft cheese.

Features - can present in a variety of ways

- · diarrhoea,
- flu-like illness
- pneumonia,
- meningoencephalitis
- ataxia and seizures

Investigations

- Suspected Listeria infection should be investigated by taking blood cultures.
- CSF may reveal a pleocytosis, with 'tumbling motility' on wet mounts

Management

- Listeria is sensitive to amoxicillin/ampicillin (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

In pregnant women

- pregnant women are almost 20 times more likely to develop listeriosis compared with the rest of the population due to changes in the immune system
- · fetal/neonatal infection can occur both transplacentally and vertically during child birth
- · complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- · treatment is with amoxicillin

Campylobacter

Overview

- Campylobacter is the commonest bacterial cause of infectious intestinal disease in the UK.
- The majority of cases are caused by the Gram-negative bacillus Campylobacter jejuni.
- It is spread by the faecal-oral route
- has an incubation period of 1-6 days.

Features

- · prodrome: headache malaise
- · diarrhoea: often bloody
- · abdominal pain

Management

- · usually self-limiting
- the most appropriate therapy is IV fluids. appropriate fluid replacement and anti-emetics are initially indicated - most units advocate no antibiotic treatment.
- the BNF advises treatment if severe or the patient is immunocompromised. Clinical Knowledge summaries also recommend antibiotics if severe symptoms (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week
- the first-line antibiotic is **clarithromycin**

Complications

- Guillain-Barre syndrome may follow Campylobacter jejuni infections
- Reiter's syndrome
- · septicaemia,
- · endocarditis,
- arthritis

Shigella

Overview

- Shigella dysenteriae is a gram negative bacillus.
- Shigellosis is the bacillary dysentery caused by Shigella dysenteriae.
- causes bloody diarrhoea, abdo pain
- The most common signs of Shigella dysentery include colitis, malnutrition, reactive arthritis, and central nervous system problems.
- severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease
- treat with ciprofloxacin

Escherichia coli

- Escherichia coli is a facultative anaerobic, lactose-fermenting, **Gram negative rod** which is a normal gut commensal.
- E. coli infections lead to a variety of diseases in humans including:
 - ⇒ diarrhoeal illnesses
 - ⇒ UTIs
 - ⇒ neonatal meningitis

Serotypes

E. coli may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
0	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to <i>E. coli</i> is usually caused by a serotype that contains the capsular antigen K-1
Н	Flagellin	

E. coli O157:H7 (enterohemorrhagic E. coli, EHEC):

- is a particular strain associated with severe, haemorrhagic, watery diarrhoea.
- It has a high mortality rate and can be complicated by haemolytic uraemic syndrome.
- It is often spread by contaminated ground beef.
- the diagnostic test is: Stool culture on sorbitol-MacConkey medium

multiple drug resistant Escherichia coli:

- mechanism of resistance → Extended spectrum beta-lactamase (ESBL) production
 - ⇒ Some *E. coli* isolates produce an Extended spectrum beta-lactamase (ESBL) that inactivates second and third generation cephalosporins.
- The class of drugs that will most reliably treat these infections are the carbapenems.
- Extended spectrum B-lactamase (ESBL) producing organisms are typically resistant
 to penicillins and cephalosporins and as such the carbapenem class of antibiotics
 are typically first line although nitrofurantoin or fosfomycin are also frequently
 effective.
- ESBL producers are most commonly *Escherichia coli* (E. coli) and *Klebsiella* species.

Which virulence factor contributes to the pathophysiology of the (E. coli) causing UTI? → P pilus

 Uropathogenic E. coli utilize a P pilus to bind to uroepithelial cells and colonize the urethra.

Incubation periods

Questions may either ask directly about incubation periods or they may be used to provide a clue in a differential diagnosis.

Less than 1 week 1 - 2 weeks		2 - 3 weeks	Longer than 3 weeks
meningococcusdiphtheriainfluenzascarlet fever	malariadengue fevertyphoidmeasles	mumpsrubellachickenpox	 infectious mononucleosis cytomegalovirus viral hepatitis HIV

Virulence factors

- Bacteria employ a large number of virulence factors which enable them to colonize the host and evade/suppress the immune response.
- The table below shows a select number of virulence factors which are important for the exam.

Virulence factor	Example organisms
IgA protease	Streptococcus pneumoniae Haemophilus influenzae Neisseria gonorrhoeae
M Protein	Streptococcus pyogenes
Polyribosyl ribitol phosphate capsule	Haemophilus influenzae
Bacteriophage	Corynebacterium diphtheriae
Spore formation	Bacillus anthracis Clostridium perfringens Clostridium tetani
Lecithinase alpha toxin	Clostridium perfringens
D-glutamate polypeptide capsule	Bacillus anthracis
Actin rockets	Listeria monocytogenes

New Delhi metallo-beta-lactamase 1

- ⇒ is the mutation that leads to carbapenem resistance.
- ⇒ Typically found in Klebsiella pneumoniae, Escherichia Coli (E. Coli), Enterobacter cloacae and others.
- ⇒ First line of management is the old antibiotic **colistin** and second line may be **tigecycline**.

D-alanyl-D-lactate

- ⇒ D-alanyl-D-lactate variation leading to loss of affinity to antibiotics is the mechanism of VRE (vancomycin resistant enterococci).
- ⇒ Vancomycin binds to D-ala-D-ala.

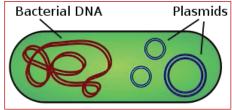
MexAB-OprM efflux pumps

➡ The presence of MexAB-OprM efflux pumps is one of the mechanisms by which pseudomonas aeruginosa is resistant to -lactams, chloramphenicol, fluoroquinolones, macrolides, novobiocin, sulfonamides, tetracycline, and trimethoprim.

penicillin binding protein 2

- Alteration to the penicillin binding protein 2 is the mechanism behind methicillinresistant staphylococcus aureus.
- Mutations in the MEC gene which codes the penicillin binding proteins give staphylococcus aureus its resistance.

Plasmids



- **Plasmid** is a small DNA molecule within a cell, separated from a chromosomal DNA and can replicate independently.
- Plasmids carry genes that may benefit the survival of the organism, for example antibiotic resistance.
- Bacteria develop resistance to antibiotics by gaining genes that encode for particular proteins that offer protection to the organism.
- Sometimes this is by mutation and at other times the gene may be acquired from another bacterial species.
- The genes are usually found in plasmids circular segments of DNA separate from the bacterial chromosome.
- Plasmids can be used to clone genes by splicing a particular gene into a plasmid and then allowing the bacteria to multiply - this is then called recombinant plasmid DNA.
- Plasmids can easily spread from one bacteria to another a sort of resistance package that bacteria can share.
- Which best explains the loss of antibiotic resistance in bacterial strain?
 - → Loss of a plasmid containing the resistance gene

Antibiotic resistance mechanism

Antibiotic	Resistance mechanism	
fluoroquinolones (eg:	Change in the bacterial DNA gyrase due to	
ciprofloxacin)	genetic mutation	
Macrolides (eg: Erythromycin)	Bacterial ribosomal methylation	
Tetracycline	Bacterial efflux of antibiotic	
chloramphenicol	Antibiotic inactivation by acetyltransferase	
Penicillin	Production of penicillinase by the bacteria is the most common mechanism of bacterial resistance to penicillin.	
	However, penicillin resistance in streptococcus pneumonia is due to alteration in the penicillin-binding protein, not production of penicillinase.	
Vancomycin	D-ala-D-ala mutates to D-ala-D-lac	

Tetanus

Definition

 Tetanus is a life-threatening neurological syndrome characterised by tonic muscle spasms and hyperreflexia, caused by the exotoxin of *Clostridium tetani*, a gram-positive sporeforming obligate anaerobe.

Incubation period: 3 - 21 days. Pathophysiology

- C. tetani spores contaminate a wound (especially with animal feces and soil) → production
 of the neurotoxins tetanospasmin and tetanolysin
- Tetanospasmin: reaches the CNS through retrograde axonal transport → cleaves a synaptobrevin protein → prevention of inhibitory neurotransmitters (i.e., GABA and glycine) → tetanic spasms.
- Tetanolysin: causes hemolysis and has cardiotoxic effects
- The wound is often unnoticed (the absence of a wound does not exclude tetanus).

Features

- Generalized tetanus: painful muscle spasms and rigidity
 - ⇒ **Trismus**: lockjaw due to spasms of jaw musculature
 - ➡ Risus sardonicus: sustained facial muscle spasm that causes a characteristic, apparently sardonic grin and raised eyebrows
 - Opisthotonus: backward arching of spine, neck, and head caused by spasms of the back muscles
 - ⇒ Dysphagia
- Life-threatening complications
 - ⇒ Laryngospasm and/or respiratory muscles spasms → respiratory failure

⇒ Autonomic dysfunction: manifest early as irritability, restlessness, sweating, and tachycardia.

Diagnosis

 clinical diagnosis based on muscle spasms and rigidity associated with an entry point for bacteria and an inadequate vaccination history.

Management

- Supportive therapy: e.g. ventilatory support, benzodiazepines and muscle relaxants
- Immunization
 - ⇒ Passive immunization → **Human tetanus immunoglobulin (HTIG)**
 - Should be given to:
 - patients with contaminated wounds who did not completed 3 doses of tetanus vaccine or unknown.
 - patient with High-risk tetanus-prone wounds who did completed 3 doses of tetanus vaccine, but last dose > 10 years ago.
 - Clean and minor wounds do not require HTIG.
 - ⇒ Active immunization → Tetanus toxoid-containing vaccine (TT)
 - For ANY wound if vaccination history is incomplete or unknown
 - For contaminated wounds ONLY if completed 3 doses of TT, but last dose > 10 years ago.
- · Wound cleaning and debridement
- Antibiotics: <u>Metronidazole</u> is now preferred to benzylpenicillin as the antibiotic of choice (500 mg intravenously every six to eight hours for 7 to 10 days).

Post-exposure tetanus prophylaxis

Post-exposure tetanus prophylaxis			
Vaccination history & wound status	Clean wounds	Tetanus-prone wounds	High-risk tetanus-prone wounds
	Clean cuts	 Contaminated puncture-type injuries wounds containing foreign bodies compound fractures wounds or burns with systemic sepsis certain animal bites and scratches 	 heavy contamination with materials likely to contain tetanus spores e.g. soil, manure. wounds or burns that show extensive devitalised tissue wounds or burns that require surgery that is delayed > 6 hours.
Unknown or < 3 TT doses	TT vaccine	TT vaccine + HTIG	TT vaccine + HTIG
≥ 3 TT doses and last dose within 10 years	None required	None required	None required
≥ 3 TT doses, but last dose > 10 years ago	None required	TT vaccine	TT vaccine + HTIG

TT: Tetanus toxoid. HTIG: Human Tetanus Immuno-Globulin

Reference: The green book, Guidance, From UK Health Security Agency January 2020 https://www.gov.uk/government/publications/tetanus-the-green-book-chapter-30

Tetanus vaccination

- Tetanus vaccine is currently given in the UK as 5 doses at: 2 months, 3 months, 4 months, 3-5 years and 13-18 years.
- Tetanus toxoid is only available in combination with other antigens such as diphtheria and pertussis.
 - ⇒ For age < 7, the DTaP (Diphtheria/Tetanus/acellular Pertussis vaccine) vaccine is given.</p>
 - ⇒ After age 7, all tetanus vaccines are paired with a lower concentration of diphtheria as signified by the lower-case "d" in the vaccination names, Tdap (Tetanus/low-dose diphtheria/acellular pertussis vaccine) or Td (Tetanus/diphtheria) may be used for booster. Td is used when the pertussis vaccine component is contraindicated.
 - ⇒ For pregnant women, one dose of the **TdaP** vaccine should be administered during **each pregnancy** between 27 weeks and 36 weeks of gestation, regardless of when the last dose of Td or Tdap was given.
 - ⇒ If a tetanus booster is indicated for wound management during pregnancy, **Tdap** should be administered instead of Td if the woman has not received Tdap previously.

Patients with large or dirty wounds and an uncertain vaccination history should be offered tetanus toxoid containing vaccination as well as Human tetanus-specific immune globulin (HTIG).

If the patient with a clean non-tetanus-prone wound has a complete vaccination history and is less than 10 years since the last dose, no prophylaxis should be given.

MRCP-1- exam - January 2015: H/O 4 cm laceration to the dorsum of left hand after cutting using a Stanley knife. no sign of a foreign body. He has 'no idea' about his tetanus vaccination. What is the most appropriate action with respect to tetanus?

- → Requires tetanus vaccine + complete vaccine course at a later date
 - (This wound is not high risk for tetanus)

Salmonella & Typhoid fever

Humans are the main reservoir for Salmonella typhi

Bacteriology

- Gram negative rods
- grow under both an aerobic and anaerobic conditions.
- · not normally present as commensals in the gut.
- Incubation period
 - ⇒ 5–30 days (most commonly 7–14 days)
- Transmission:
 - ⇒ fecal-oral

Types

- Salmonella typhi causes Typhoid
- Salmonella paratyphi (types A, B & C) causes paratyphoid
 - ⇒ They are often termed enteric fevers.
 - ⇒ Blood and bone infections caused by non-typhi salmonella (NTS) are typically associated with malaria and homozygous sickle cell disease, especially in

children. The reason for this perceived susceptibility is not fully understood - but it may be in part due to the haemolysis and subsequent iron availability to the bacteria, which is 'siderophilic' in nature.

Pathophysiology

- Lifecycle
 - 1. Oral uptake of pathogen
 - 2. Distal ileum: migration into the Peyer patches
 - 3. Infection of macrophages and reticuloendothelial system → nonspecific symptoms
 - 4. Spread from macrophages to the bloodstream: septicemia → systemic disease
 - 5. Migrates back to intestine → excretion in feces

Typhoid vaccines

- typhoid vaccines are currently available
 - ⇒ (Typhoid vaccine does not protect from paratyphoid infection)
- There are 3 types of typhoid vaccine:
 - 1. parenteral (Typh-I), → inactivated vaccine (i.e. killed)
 - 2. parenteral combined with hepatitis A (HA-Typh-I), and
 - 3. oral (Typh-O) → Live-attenuated vaccine
- These vaccines provide approximately **50% protection** against clinical disease.
- No vaccine is available against paratyphoid fever.
- Vaccinated individuals who develop the disease will have a higher threshold but the same disease.

Features

- initially systemic upset (headache, fever, arthralgia)
- · relative bradycardia
- abdominal pain, distension
- diarrhoeal disease
 - Yellow-green diarrhea, comparable to pea soup (caused by purulent, bloody necrosis of the Peyer patches)
- constipation:
 - although Salmonella is a recognised cause of diarrhoea, constipation is more common in typhoid
 - ⇒ obstipation and ileus (as a result of swollen Peyer patches in the ileum)
- Rose spots:
 - ⇒ present on the trunk in 40% of patients,
 - حول السرة (most commonly around the navel)
 - ⇒ more common in paratyphoid
- Neurological symptoms (delirium, coma)
- Rarely causes sepsis, meningitis, myocarditis, and renal failure

Complication

- Chronic Salmonella carrier
 - ⇒ Definition:
 - positive stool cultures 12 months after overcoming the disease
 - ⇒ Incidence:
 - up to 6% of the patients become chronic carriers
 - ⇒ Presentation:
 - typically asymptomatic
 - ⇒ Treatment:
 - fluoroquinolones (e.g., ciprofloxacin) administered for at least 1 month
 - ⇒ Chronic carriers are not allowed to work in the food industry.
 - ⇒ Increased risk for cholangiocarcinoma (bile duct cancer)

Investigations

- normal or low leukocyte count with eosinopenia
- Blood culture.
 - ⇒ the most effective investigation for diagnosis
 - ⇒ (should be done prior to starting antibiotic)
- Bone marrow culture
 - ⇒ highly sensitive diagnostic test even in later stages of infection after antibiotic therapy has begun.
 - ⇒ indicated for all patients with prolonged pyrexia if routine investigations have not provided a diagnosis.
- in chronic carriers
 - ⇒ **Blood cultures** will be **negative** in chronic carriers because the organism resides mainly in the gallbladder.
 - ⇒ Salmonella typhi can be cultured from intestinal secretions, faeces or urine
- Widal's test
 - ⇒ Serological test
 - ⇒ poor sensitivity
 - ⇒ negative in early infection.
 - indicated only after 5 to 7 days of fever.
 - ⇒ not useful for detecting chronic carriage.
- Faecal culture
 - ⇒ positive in only 50% of cases during the first week of illness.

Complications

- osteomyelitis
 - ⇒ (especially in sickle cell disease where Salmonella is one of the most common pathogens)
- GI bleed/perforation
- meninaitis
- cholecystitis
- chronic carriage (1%)
 - ⇒ more likely if adult females)

Treatment

- best treated with guinolones, chloramphenicol or cotrimoxazole.
- However, with breast feeding chloramphenicol is relatively contraindicated as are quinolones due to potential risk even if small.
- Also, cotrimoxazole is safe in breast feeding except with infants less than 2 months due to possible risk of increased bilirubin.
- In pregnancy or children, the drug of choice is parenteral ceftriaxone.
- The gallbladder may act as a reservoir of infection and cause relapse in individuals treated with antibiotics. Cholecystectomy may be indicated.
- According to the NICE guidelines, anyone above the age of 50, immunocompromised or
 has cardiac valve disease/endovascular abnormalities should be treating empirically with
 ciprofloxacin 500mg BD when they have been diagnosed with nontyphoidal Salmonella gastroenteritis.

Meningitis

Causes

The most common cause of bacterial meningitis is Streptococcus pneumoniae (Gram positive diplococci), accounting for >50% cases.

Listeria is a less common Gram positive cause of meningitis.

0 - 3 months	3 months - 6 years	6 years - 60 years	> 60 years	Immunosuppres sed
Group B Streptococcus (most common cause in neonates)		Neisseria meningitides	Streptococcus pneumoniae	Listeria monocytogenes
E. coli	Streptococcus pneumoniae	Streptococcus pneumoniae	Neisseria meningitides	
Listeria monocytogenes	Haemophilus influenzae		Listeria monocytogenes	

Coxsackie virus is the most common viral cause of meningitis.

Pneumococcal meningitis

- caused by the Gram positive coccus *Strep. pneumoniae*.
- the second commonest cause of bacterial meningitis (commonest in the elderly)
- associated with the highest mortality (20%) and highest morbidity, such as deafness which may occur in 50% (Nerve deafness is a common complication)
- Chronic adhesive arachnoiditis is a complication of pneumococcal meningitis characterized by fibrosis of the arachnoid granulations.
- Contacts do not require treatment
- there is no rash associated with pneumococcal meningitis.

In the context of septic meningitis, the petechial rash is diagnostic for infection with Neisseria meningitidis

Listeria meningitis

- · Risk factors for listeria meningitis include
 - ⇒ neonates
 - ⇒ Older age
 - ⇒ immunosuppression.
- It is typically associated with brainstem signs.

- Beta-hemolysis is the type of hemolysis exhibited by <u>Listeria monocytogenes</u>, an organism showing tumbling motility that causes meningitis in newborns.
- Cerebrospinal fluid shows:
 - ⇒ Neutrophilic pleocytosis
 - ⇒ Low glucose, and
 - ⇒ High protein.

Fungal meningitis

- Patients at risk for fungal **meningitis** include:
 - ⇒ those who are significantly immunocompromised,
 - those who have received intrathecal injections in the past.
- Cerebrospinal fluid analysis
 - ⇒ elevated opening pressure
 - ⇒ detectable b-D-glucan
- Testing for <u>b-D-glucan</u> has been an approved blood test to detect systemic fungal infection.

Partially treated bacterial meningitis

Partial treatment of bacterial meningitis can result in <u>false negative CSF culture</u> and <u>Gram stain</u>, but the CSF white cell count should be unaffected.

- The assessment of children with suspected bacterial meningitis who have already received antibiotic therapy from their GP is a common diagnostic problem.
- Partial treatment may reduce the incidence of positive CSF Gram stains to less than 60%, and it also reduces the ability to grow the bacteria, particularly meningococcus.
 - > Partial treatment may induce:
 - negative CSF culture
 - negative Gram stain
- CSF glucose, protein, neutrophils and bacterial antigen testing or polymerase chain reaction (PCR) should be completely unaffected.
- A normal white cell count would make the diagnosis very unlikely.
- In normal CSF the glucose is usually > 65% of blood glucose.

Meningitis: Investigations

- Investigations suggested by NICE
 - ⇒ full blood count
 - ⇒ CRP
 - ⇒ coagulation screen
 - ⇒ blood culture
 - ⇒ whole-blood PCR
 - ⇒ blood glucose
 - ⇒ blood gas
 - ⇒ Lumbar puncture if no signs of raised intracranial pressure

Meningitis: CSF analysis

Mumps meningitis is associated with a low CSF glucose

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in

meningitis:

	Bacterial	Viral	Tuberculous
Appearance	Cloudy	Clear/cloudy	Slight cloudy, fibrin web
Glucose	Low (< 1/2 plasma)	60-80% of plasma glucose*	Low (< 1/2 plasma)
Protein	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
White cells	10 - 5,000 polymorphs/mm³	15 - 1,000 lymphocytes/mm³	10 - 1,000 lymphocytes/mm³

^{*}mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

- The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)
- Bacterial culture of cerebrospinal fluid is the gold-standard test for determining
 if a case of meningitis is bacterial in etiology

The CSF lymphocytosis combined with a glucose greater than half the serum level points towards a viral meningitis.

Management

In patients presenting with symptoms and signs of meningitis, treat empirically for bacterial meningitis while awaiting test results from the lumbar puncture.

- All patients should be transferred to hospital urgently.
- If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then intramuscular benzylpenicillin may be given, as long as this doesn't delay transit to hospital.
- In bacterial meningitis, dexamethasone should also be given with the first dose of antibiotics.

BNF recommendations on antibiotics

Scenario	BNF recommendation
Initial empirical therapy aged < 3 months	Intravenous cefotaxime + amoxicillin
Initial empirical therapy aged 3 months - 50 years	Intravenous cefotaxime
Initial empirical therapy aged > 50 years	Intravenous cefotaxime + amoxicillin
Meningococcal meningitis	Intravenous benzylpenicillin or cefotaxime
Pneuomococcal meningitis	Intravenous cefotaxime
Meningitis caused by Haemophilus influenzae	Intravenous cefotaxime
Meningitis caused by Listeria	Intravenous amoxicillin + gentamicin

- If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using chloramphenicol.
- Ceftriaxone does not cover Listeria well, and in the over 60s or immunosuppressed, amoxicillin should be added in to empirical meningitis management to cover this.

Management of contacts

- prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis
- oral ciprofloxacin or rifampicin may be used.
 - ⇒ The BNF recommends a twice a day dose of rifampicin for two days, based on the patients weight.
 - ⇒ The Health Protection Agency (HPA) guidelines now state that whilst either
 may be used ciprofloxacin is the drug of choice as it is widely available
 and only requires one dose
 - ➡ Rifampicin may reduce the efficacy of the oral contraceptive through liver enzyme induction. So not preferred in sexually active. Therefore ciprofloxacin would be the most appropriate agent as it does not induce cytochrome p450.
- the risk is highest in the first 7 days but persists for at least 4 weeks
- meningococcal vaccination should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy
- for pneumococcal meningitis no prophylaxis is generally needed. There are
 however exceptions to this. If a cluster of cases of pneumococcal meningitis occur
 the HPA have a protocol for offering close contacts antibiotic prophylaxis.

September 2010 exam. A 57-year-old female presents with headache, fever, neck stiffness with a positive Kernig's sign. CSF culture: Gram positive bacilli. What is the most likely causative organism?

→ Listeria monocytogenes

MRCPUK-parat-1-January 2013 exam: A 47-year-old lady with Feature of fever, headache and nuchal rigidity. Lumbar puncture reveals: Appearance: Cloudy. Glucose:1.7 mmol/l. Protein:1.9 g/l. White cells: 900 / mm³ (90% polymorphs). What is the most likely infective agent?

- → Streptococcus pneumoniae
 - (CSF →results bacterial meningitis (low glucose, high protein, high polymorphs).
 - In this age group Streptococcus pneumoniae and Neisseria meningitidis are the most common causes of bacterial meningitis)

MRCPUK-parat-1-May 2014 exam: A diagnosis of pneumococcal meningitis is made. There are no other reports of meningitis in the local area over the past 4 weeks. How should the close contacts of this boy be managed?

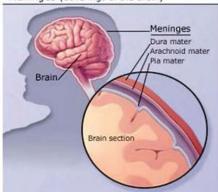
→ No action is needed (unless cluster of cases develop)

MRCPUK-parat-1-May 2009 exam: A 23-year-old man is admitted with purpuric rash, pyrexia and confusion. His GP had given him intramuscular benzylpenicillin. Which one of the following investigations is most likely to reveal the diagnosis?

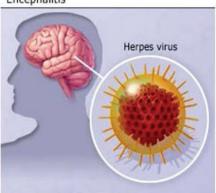
- → Blood PCR for meningococcus
 - (The blood cultures are likely to be negative as antibiotics have already been given. PCR has a sensitivity of over 90%)

Encephalitis

Meninges (Coverings of the Brain)







Encephalitis usually presents with altered mental status, erratic behavior, etc (brain parenchyma involved).

Aetiology

• The most common cause is herpes simplex, usually type I (HSV-1).

Clinical Presentation

- Altered mental status with fever and headache is the diagnosis.
- Neck stiffness similar to that found in meningitis can occur, making it difficult to distinguish encephalitis from meningitis.
- Seizures may also occur.

Diagnosis

- Although CT or MRI scan of the head should be performed, it cannot give a specific diagnosis. HSV has a predilection for involvement of the temporal lobes, which can sometimes be seen on CT.
- A lumbar puncture is the key to the diagnosis.
- PCR (polymerase chain reaction) for HSV has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy.

Treatment

- HSV encephalitis is best treated with IV acyclovir.
- Acvclovir-resistant herpes is treated with foscarnet

Meningococcal septicaemia

Overview

- It is associated with a high morbidity and mortality unless treated early
- meningococcal disease is the leading infectious cause of death in early childhood.
- · A high index of suspicion is therefore needed.

Presentation of meningococcal disease:

- 15% meningitis
- 25% septicaemia
- 60% a combination of meningitis and septicaemia

Investigations

- blood cultures
- blood PCR
- · lumbar puncture is usually contraindicated
- full blood count and clotting to assess for disseminated intravascular coagulation

Management

 the most important initial step → administration of intravenous antibiotics (cefotaxime) is the greatest priority, regardless of whether cultures have been sent.

Sepsis

Overview

- Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection.
- Sepsis with shock is a life-threatening condition that is characterised by low blood pressure despite adequate fluid replacement, and organ dysfunction or failure.

Definition

- The new definition attempts to draw upon up-to-date pathobiology and distinguish between sepsis and uncomplicated infection. A new tool has been developed for this purpose - the SOFA or qSOFA.
 - ⇒ The gSOFA (Quick SOFA) criteria are:

- Respiratory rate > or equal to 22/min
- Altered GCS
- Systolic blood pressure < or equal to 100mmHg
- Septic shock is defined as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. This changes from the previous definition to recognise the importance of cellular abnormalities.
- Septic shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Risk factors for sepsis

- Age (< 1 year and > 75 years)
- very frail people
- Immunocompromised
 - ⇒ impaired immune function (eg, DM, splenectomy, sickle cell disease)
 - ⇒ drugs(long-term steroids, chemotherapy, immunosuppressant)
- surgery, or other invasive procedures, in the past 6 weeks
- any breach of skin integrity (eg, cuts, burns, blisters or skin infections)
- misuse drugs intravenously
- indwelling lines or catheters

Risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis

High risk criteria	Moderate to high risk criteria
Objective evidence of new altered mental state	 History from patient or relative of new onset of altered behaviour or mental state History of acute deterioration of functional ability Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks
 respiratory rate: ≥ 25 breaths per minute New need for oxygen (more than 40% FiO₂) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease) 	Raised respiratory rate: 21–24 breaths per minute
Systolic blood pressure ≤ 90 mmHg or more than 40 mmHg below normal	Systolic blood pressure 91–100 mmHg
heart rate: > 130 beats per minute	heart rate: 91–130 beats per minute (for pregnant women 100–130 beats per minute) or new onset arrhythmia
Not passed urine in previous 18 hours. For catheterised patients, passed less than 0.5 ml/kg of urine per hour	Not passed urine in the past 12–18 hours For catheterised patients, passed 0.5– 1 ml/kg of urine per hour
- Mottled or ashen appearance	Tympanic temperature less than 36°C Signs of potential infection, including
Mottled or ashen appearanceCyanosis of skin, lips or tongueNon-blanching rash of skin	redness, swelling or discharge at surgical site or breakdown of wound.

Low risk criteria:

- Normal behavior
- No high risk or moderate to high risk criteria met

Temperature in suspected sepsis

- Do not rely on fever or hypothermia to rule sepsis either in or out.
- Some people with sepsis may not develop a raised temperature:
 - ⇒ older or very frail
 - ⇒ severely ill
 - ⇒ people having treatment for cancer
 - ⇒ young infants or children.
- a rise in temperature can be a physiological response (eg: after surgery or trauma).

Management

- . 1 or more high risk criteria:
 - ⇒ **blood test** for blood gas including glucose and lactate measurement, blood culture, full blood count, C-reactive protein, urea and electrolytes, creatinine, clotting screen.
 - Sepsis may be complicated by disseminated intravascular coagulation

- ⇒ give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour)
- Any high risk criteria and lactate > 4 mmol/litre, or systolic BP < 90 mmHg:
 - ⇒ I.V fluid bolus without delay (within 1 hour)
 - ⇒ refer to critical care for review of management including need for central venous access , inotropes or vasopressors.
- Any high risk criteria and lactate between 2 and 4 mmol/litre: I.V fluid bolus without delay (within 1 hour)
- ⇒ Any high risk criteria and lactate < 2 mmol/litre: consider I.V fluid bolus
- Failure to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation
 - ⇒ Failure to respond is indicated by any of:
 - systolic blood pressure persistently below 90 mmHg
 - reduced level of consciousness despite resuscitation
 - respiratory rate over 25 breaths per minute or a new need for mechanical ventilation
 - lactate not reduced by more than 20% of initial value within 1 hour.
- 2 or more moderate to high risk criteria
 - ⇒ blood test for blood gas including glucose and lactate measurement, blood culture, full blood count, C-reactive protein, urea and electrolytes, creatinine
 - ⇒ review the person's condition and venous lactate results within 1 hour
- 2 or more moderate to high risk criteria and lactate > 2 mmol/litre or evidence of acute kidney injury: treat as high risk
- 2 or more moderate to high risk criteria, have lactate < 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:
 - ⇒ repeat structured assessment at least hourly
 - ⇒ review by a senior within 3 hours for consideration of antibiotics.
- 2 or more moderate to high risk criteria, have lactate < 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated:
 - ⇒ manage the definitive condition
 - ⇒ if appropriate, discharge
- Intravenous fluids in people with suspected sepsis
 - ⇒ If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of 500 ml over less than 15 minutes.

Sepsis Resuscitation Bundle: Surviving Sepsis Campaign

- Should begin immediately, but must be accomplished within the first six hours of presentation.
 - Serum lactate measured.
 - 2. Blood cultures obtained prior to antibiotic administration.
 - 3. From the time of presentation, broad-spectrum antibiotics administered within three hours for ED admissions and one hour for non-ED ICU admissions.
 - 4. In the event of hypotension and/or lactate > 4 mmol/l (36 mg/dl):
 - Deliver an initial minimum of 30 ml/kg of crystalloid (or colloid equivalent).
 - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg.
 - 5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/l (36 mg/dl):
 - Achieve central venous pressure (CVP) of > 8 mm Hg.
 - Achieve central venous oxygen saturation (ScvO2) of > 70%.

H/O sepsis secondary to pneumonia. treated with 4.5 L sodium chloride 0.9%. blood pressure was 82/40 mmHg. In attempting to restore the blood pressure, what is the most appropriate intravenous therapy?

→ noradrenaline (norepinephrine)

Ref: www.mrcpuk.org/ Acute Medicine Specialty Certificate Examination/ sample questions

Tuberculosis (TB)

Definition

- TB is an infection caused by *Mycobacterium tuberculosis* that most commonly affects the lungs.
- Mycobacterium tuberculosis:
 - ⇒ aerobic non-motile bacillus.
 - ⇒ classified as a Gram-positive organism

Pathophysiology

- Primary tuberculosis
 - ➤ Bacilli are transported via lymphatics early in the disease process to regional lymph nodes to cause marked lymphadenopathy.
 - Process after exposure to mycobacterium tuberculosis:
 - 90 % of individuals with <u>intact immunity</u> control further replication of the bacilli, by either:
 - Clearance or
 - enter a "latent" phase (asymptomatic, but has the potential to become active at any time)
 - 10% → Progression to local pulmonary disease or dissemination
 - occurs more frequently in those with <u>poor immune responses</u>, such as:
 - ⇒ HIV
 - ⇒ chronic kidney failure,
 - ⇒ poorly controlled diabetes mellitus,

- ⇒ immunosuppressive medications (including transplant recipients),
- ⇒ young children (before the age of five),
- ⇒ older adults.
- non-immune host who is exposed to M. tuberculosis may develop primary infection of the lungs. A small lung lesion known as a Ghon focus develops. The Ghon focus is composed of tubercle-laden macrophages. The combination of a Ghon focus and hilar lymph nodes is known as a Ghon complex
- in **immunocompetent** people the initial lesion usually heals by fibrosis.
- immunocompromised peoples may develop disseminated disease (miliary tuberculosis).
 - Mycobacterium avium causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm³.
- Pleural and pericardial infections (which can result in effusions) occur at or shortly after primary infection.
- Secondary (post-primary) tuberculosis
 - ⇒ Definition
 - Reactivation of the initial infection if the host becomes immunocompromised
 - ⇒ Site of reactivation:
 - Pulmonary: the most common site for secondary TB.
 - generally, occurs in the <u>apex of the lungs</u> and may spread locally or to more distant sites.
 - Extra-pulmonary:
 - CNS (tuberculous meningitis the most serious complication)
 - Vertebral bodies (Pott's disease)
 - Cervical lymph nodes (Scrofuloderma)
 - ⇒ Scrofuloderma occurs when the skin becomes involved by direct extension from an underlying tuberculous infection (usually lymphadenitis).
 - Renal
 - GIT
 - ⇒ Causes of immunocompromise:
 - immunosuppressive drugs (e.g. Steroids)
 - HIV
 - malnutrition

Features

- Primary TB is usually asymptomatic
- cough >2 to 3 weeks' duration, lymphadenopathy, fevers, night sweats, weight loss
- Pulmonary complications of TB can include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, malignancy, and chronic pulmonary aspergillosis.
- TB may be associated with an inflammatory polyarthritis that may follow a similar pattern to rheumatoid arthritis

Transmission

Non-sputum producing patients are non-infectious. Only untreated smear-positive pulmonary TB is likely to be infectious.

Screening

- Mantoux test
- Interferon-gamma blood test
 - ⇒ It is used in several specific situations such as:
 - the Mantoux test is positive or equivocal
 - people where a tuberculin test may be falsely negative (see below)

Patients should be routinely screened for TB exposure before treatment with Etanercept with the tuberculin skin test

Mantoux test (tuberculin test) (purified protein derivative (PPD) test)

- Mechanism:
 - ⇒ It is a **type IV**, (delayed) hypersensitivity reaction.
 - ⇒ It is a cell mediated immune response (measures the T cell-mediated immune response to TB antigen)
 - mediated by interferon-γ secreted by T_h1 cells which in turn stimulates macrophage activity.

 - ⇒ Positive tuberculin test occurs between three weeks and three months after primary infection.
- Indication:
 - ⇒ the main technique used to screen for latent tuberculosis.
 - ⇒ The most commonly used screening test for contacts of a patient with recently diagnosed TB
- Method
 - ⇒ 0.1 ml of 1: 1,000 purified protein derivative (PPD) injected intradermally
 - ⇒ result read 2-3 days later
 - ⇒ The left forearm is typically used.
- Interpretation
 - ⇒ Only the induration, not surrounding erythema, is used in the measurement and the longest diameter is measured in millimeters:

Diameter of induration	Positivity	Interpretation
< 6mm	Negative - no significant hypersensitivity to tuberculin protein	Previously unvaccinated individuals may be given the BCG
6 - 15mm	Positive - hypersensitive to tuberculin protein	Should not be given BCG. May be due to previous TB infection or BCG or atypical mycobacteria. However, in other contexts (e.g. immigrant screening and contact tracing), further investigation and follow-up may be indicated.
> 15mm	Strongly positive - strongly hypersensitive to tuberculin protein	Suggests tuberculosis infection → do chest x-ray

- ⇒ **False negative tests may be caused** by: (→ \preaction to tuberculin protein)
 - miliary TB
 - sarcoidosis
 - immunosuppression (HIV, corticosteroids)
 - lymphoma
 - very young age (e.g. < 6 months)
 - Viral infections,
 - live viral vaccines
 - poor nutrition.
- ⇒ Active disease may be indicated by grade III/IV response to tuberculin.
- ⇒ 8% of individuals with history of BCG vaccination have grade I/II response.

Which cytokines is most involved in the response of a Mantoux test?

⇒ Interferon-v

BCG

- Definition
 - ⇒ a live attenuated vaccine derived from a strain of *Mycobacterium*. *bovis*.
- Benefits
 - ⇒ BCG is 70-80% effective against severe TB infection.
 - ⇒ Protection is thought to last for **10-15 years**, with greater efficacy in the under 16 years population.
 - ⇒ it also has effects against leprosy (Mycobacterium (M. leprae)) (up to 80% protection)
 - ⇒ BCG is currently used as a form of immunotherapy for treating bladder cancer; which can lead to disseminated *M. bovis* infection (systemic 'BCG-it is')
- Indications
 - ⇒ should be given to neonates in high risk groups.
 - ⇒ Previously unvaccinated individuals
 - A Mantoux should be documented before administration.

- It should not be given to children who have a strongly positive tuberculin test
- new entrants from high- incidence countries and are previously unvaccinated (that is, without adequate documentation or a BCG scar) and are aged:
 - younger than 16 years or
 - ❖ 16–35 years from sub- Saharan Africa or a country with a TB incidence of 500 per 100,000 or more.
- ⇒ healthcare workers
- ⇒ Mantoux- negative contacts of people with pulmonary and laryngeal TB if they:
 - have not been vaccinated previously and are aged
 - 35 years or younger or
 - are aged 36 years and older and a healthcare or laboratory worker who has contact with patients or clinical materials.

Contraindications

- ⇒ BCG is a life attenuated vaccine containing M bovis, it should therefore be avoided in the immunosuppressed population.
 - In case of increased risk of HIV, NICE advises that an HIV test should be done prior to vaccination.

Diagnosis

definitive diagnosis

- ⇒ isolation of Mycobacterium tuberculosis from a bodily secretion (eg, culture of sputum, bronchoalveolar lavage, or pleural fluid) or tissue (pleural biopsy or lung biopsy).
- ⇒ Send multiple respiratory samples (3 deep cough sputum samples, preferably including 1 early morning sample) for TB microscopy and culture.
- ⇒ If spontaneous sputum (by coughing) is difficult:
 - Sputum may be induced by inhalation of hypertonic saline generated by a nebulizer.
 - If patient is unable to produce sputum, bronchoscopy with bronchial washings for microscopy staining and culture is the investigation of choice.
 - In children who are unable to cough up sputum, the gold standard is gastric washings for M tuberculosis culture
- ⇒ <u>Tissue biopsy</u> may establish a definitive diagnosis of TB when other diagnostic techniques are not diagnostic.
- probable diagnosis: can be based on:
 - ⇒ Typical clinical and chest X-ray findings, together with either
 - ⇒ sputum (or other specimens) positive for acid-fast bacilli,
 - stains very weakly on testing. When using the Ziehl-Neelsen test it stains bright red against a blue background.
 - ⇒ typical histopathological findings on biopsy material
- Smear-positive tuberculosis → highly infectious (Patient needs treatment and isolation from casual contacts, his close contacts need screening)
- **Culture-positive tuberculosis** means the immediate smear is negative, but prolonged culture has shown tuberculosis.

Management (NICE guidelines 2016)

- If there are clinical signs and symptoms consistent with a diagnosis of TB, start treatment without waiting for culture results.
 - ⇒ Consider completing the standard recommended regimen even if subsequent culture results are negative.
- Should only be carried out in hospitals with appropriate isolation facilities.
 - ⇒ Smear-positive tuberculosis means the patient is highly infectious to both close contacts (more than 8 hours spent together per day) and casual contacts, such as other patients on the ward and healthcare workers.
 - ⇒ He therefore needs to be isolated in a negative-pressure room,
 - contacts should wear particulate masks until he has received anti-tuberculous therapy for 2 weeks. The sputum might remain positive after this time, but the organisms will be dead.

• Length of treatment:

- ⇒ All forms of pulmonary TB may be treated equally except tuberculous pleural effusion which may require drainage (with large effusions causing breathlessness) and adjunct corticosteroids to delay reaccumulation.
- ⇒ A 6-month course of treatment is adequate for all non-CNS disease.
- ⇒ Length of treatment for other forms are:

bone TB – 6 months

- ❖ Treatment for bone and joint tuberculosis is recommended to continue for 2 months with the initial phase consisting of quadruple therapy and the remaining 4 months of dual therapy.
- It is recommended not to extend treatment for residual complications such as collapsed discs or bending of the spine, although there is some debate about this.
- meningitis 1 vear
 - Antituberculous treatment for 12 months is recommended for TB meningitis.
- drug resistance 2 years.
 - Treatment must be continued for a minimum of 18 months, with at least 9 months of treatment after the patient becomes culture-negative.

TB with strider:

- If patient of TB presents with worsening breathlessness and stridor due to mediastinal lymph nodes compressing the carina, the next step - after commencing steroid - is urgent (CT) scan, first to confirm the degree of airway compression and second to assess the response to chemotherapy.
- Patients on long term steroids with TB:
 - Patients on long term steroids should have their dose of steroids increased when starting antituberculous therapy.
 - The metabolism of corticosteroids is increased by rifampicin. (P450 inducer)
- Failing regimen in the treatment of TB:
 - ⇒ reactivation of (TB) infection during treatment course.
 - ⇒ Evidence of failing treatment:
 - worsening symptoms,
 - elevated C-reactive protein.
 - progression of chest X-ray changes
 - ⇒ what is the most appropriate next treatment step?
 - Most guidelines recommend progression to five agents rifampicin, pyrazinamide, isoniazid, ethambutol and streptomycin.

TB Drug therapy

Treatment for active tuberculosis is:

- Initial phase first 2 months (RIPE)
 - 1. Rifampicin
 - 2. Isoniazid
 - 3. Pyrazinamide
 - 4. Ethambutol
 - (the 2006 NICE guidelines now recommend giving a 'fourth drug' such as ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected)
 - either ethambutol or streptomycin.
- Continuation phase next 4 months
 - 1. Rifampicin
 - 2. Isoniazid
 - After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampicin are continued as daily or intermittent therapy for 4-or-more months.
 - Therapy must be extended if the patient has cavitary disease or remains culture positive after 2 months of treatment.

Treatment for latent tuberculosis

isoniazid alone for 6 months

Treatment for meningeal tuberculosis

- treated for a prolonged period (at least 12 months)
- 4 drugs for the first 2 months, followed by isoniazid and rifampicin 10 months.
- addition of **steroids** (equivalent to prednisolone 20-40 mg) is recommended for the first 2-3 weeks, then with gradual reduction.
 - ⇒ (use of steroids is recommended to ensure adequate brain penetration and to prevent cranial nerve compression by meningeal scarring.

Directly observed therapy

- with a three times a week dosing regimen may be indicated in certain groups, including:
 - ⇒ homeless people with active tuberculosis
 - ⇒ patients who are likely to have poor concordance
 - ⇒ all prisoners with active or latent tuberculosis

Tuberculosis: drug side-effects and mechanism of action

- Rifampicin
 - ⇒ mechanism of action:
 - inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
 - ⇒ mechanism of resistance for rifampicin resistant Mycobacterium tuberculosis
 - Mutations in rpoB gene cause alterations in the bacterial DNA dependent RNA transcriptase, which prevents the binding of rifampicin.
 - ⇒ In patients with HIV/TB co-infection:
 - Rifampicin is a potent inducer of liver enzymes (cytochrome P450).
 Furthermore, it up-regulates the expression of P-glycoprotein in the gastrointestinal tract.
 - Co-administration of a protease inhibitor with rifampicin therefore will often lead to sub-therapeutic levels of the protease inhibitor.

- the British HIV Association suggest the substitution of rifampicin for an alternative rifamycin agent (rifabutin or rifapentine), which has less inducing action of cytochrome P450
- ⇒ Side effects
 - potent liver enzyme inducer
 - hepatitis,
 - orange secretions (Red or orange discoloration of the urine and other body fluids)
 - flu-like symptoms
 - Rifampicin and isoniazid can cause a relative vitamin D deficiency

Isoniazid

- ⇒ mechanism of action:
 - Prevents cell wall synthesis by inhibiting the synthesis of mycolic acid
 - Bactericidal
- ⇒ Side effects
 - Hepatotoxicity
 - INH is the most common drug associated with toxicity.
 - INH metabolites are responsible for INH hepatotoxicity
 - N-acetyltransferase 2 (NAT2) is the primary enzyme that contributes to INH metabolism.
 - ❖ NAT2 deficiency increases the risk of INH-induced liver injury.
 - slow acetylators are prone to develop more severe hepatotoxicity than rapid acetylators.
 - Peripheral neuropathy:
 - Isoniazid-related demyelinating peripheral neuropathy
 - relatively acute onset
 - typically presents with reduced sensation +/- absent reflexes in lower limbs.
 - prevented with low dose pyridoxine (Vitamin B6)
 - treated with high-dose Pyridoxine
 - agranulocytosis
 - Drug-induced lupus erythematosus
 - liver enzyme inhibitor

⇒ isoniazid toxicity

- Risk factors
 - alcoholism
 - diabetes
 - malnutrition,
 - HIV.
 - renal failure.
 - neurotoxic medications, and
 - pregnancy.
- Treatment
 - high-dose pyridoxine, (low dose pyridoxine is used for prophylaxis).
 - stopping or reducing the dose of isoniazid
 - control of other risk factors (e.g. reduced alcohol intake, improved glycaemic control etc)

INH Injures Neurons and Hepatocytes

Pyrazinamide

- ⇒ mechanism of action:
 - converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS)
 - Bactericidal
 - Streptomycin has high activity against extracellular organisms whilst pyrazinamide have high activity against intracellular organisms.
- ⇒ side effects
 - hyperuricaemia causing gout
 - arthralgia, myalgia
 - the most common cause of arthralgia after starting antituberculous
 - Hepatotoxicity

Ethambutol

- ⇒ mechanism of action:
 - Prevents cell wall synthesis by inhibiting arabinosyltransferase (which polymerizes arabinose into arabinan)
 - Bacteriostatic
- ⇒ side effects
 - optic neuritis: check visual acuity before and during treatment
 - Ocular side-effects of ethambutol
 - Loss of acuity
 - Colour blindness
 - · Restriction of visual fields
- ⇒ dose needs adjusting in patients with renal impairment
 - Ethambutol is renally excreted and therefore dose adjustment is necessary
 to minimise the risk of toxic effects (optic neuropathy). The remaining drugs
 are mainly metabolised in the liver and can be given in normal doses in renal
 failure.
- Anti-tuberculosis drug and LFTs:
 - ⇒ All tuberculosis patients should have pre-treatment LFTs.
 - ⇒ rifampicin/isoniazid/pyrazinamide all are associated with liver toxicity, but isoniazid are most commonly implicated (this fact are tested in MRCPI website -part 1, sample question)
 - ⇒ Up to 20% of the patients receiving isoniazid either in single or combination therapy develop transient asymptomatic elevation in liver enzymes, which settle with continued use of the drug.
 - while some patients (less than 1%–3%) develop severe liver injury and even liver failure
 - ⇒ If there is no pre-existing liver disease, LFTs are only repeated (and treatment stopped) if fever, malaise, vomiting, jaundice or unexplained deterioration occurs during treatment.
 - ⇒ Regular LFTs should be performed in patients with previously known chronic liver disease.
 - ⇒ define hepatotoxicity → rifampicin/isoniazid/pyrazinamide should be stopped
 - If AST/ALT levels rise by 5 times upper limit of normal range without symptoms

- If ALT/AST levels rise by 3 times upper limit of normal range with symptoms (abdominal pain, nausea, vomiting, unexplained fatigue or jaundice)
- ⇒ If the patient is not unwell and/or has non-infectious TB, no treatment until LFT returns to normal.
- ⇒ If clinically unwell or sputum smear is positive within two weeks of starting treatment, consider streptomycin and ethambutol until LFT returns to normal.
- Once LFT is back to normal, challenge dosages can be reintroduced sequentially in order of isoniazid, rifampicin and pyrazinamide with daily monitoring of patient's condition and LFT.
- ⇒ If there is a further reaction , the offending drug should be excluded and a suitable alternative regimen used.
- Immune reconstitution disease
 - ➡ Immune reconstitution inflammatory syndrome (IRIS) (also known as immune recovery syndrome) is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse
 - ⇒ occurs typically 3-6 weeks after starting treatment
 - ⇒ often presents with enlarging lymph nodes

Latent tuberculosis infection (LTBI)

Definition

• screening tests indicating previous infection with *M. tuberculosis are* positive without any pathological findings on radiological imaging.

Epidemiology

 Approximately 30% of persons exposed to Mycobacterium tuberculosis will develop LTBI and, if untreated, approximately 5% to 10% of these persons will progress to active tuberculosis disease or reactivation of tuberculosis.

Risk for developing active tuberculosis

- The lifetime risk of reactivation TB for a person with LTBI is about 5–10%.
- Risk factors for developing active tuberculosis include:
 - ⇒ silicosis
 - ⇒ chronic renal failure
 - ⇒ HIV positive
 - ⇒ solid organ transplantation with immunosuppression
 - ⇒ intravenous drug use
 - ⇒ haematological malignancy
 - ⇒ anti-TNF treatment
 - ⇒ previous gastrectomy

Diagnosis

- Mantoux tuberculin skin test (TST)
 - ⇒ can be positive with both active and latent TB but can also by a previous BCG vaccination.
 - ⇒ Recommended for close contacts of a person with TB.

- ⇒ If positive (induration ≥ 5 mm, regardless of BCG history) → assess for active TB
- Interferon gamma release assay (IGRA)
 - □ Indications
 - Quantaferon testing (interferon gamma testing) is recommended as a secondline test for people whose Mantoux testing may be less reliable - for example, BCG-vaccinated people.
 - If the Mantoux test is positive + active TB is excluded, and evidence of infection is needed to decide on treatment. for example:
 - if the person needs enhanced case management or
 - if there could be adverse events from treatment.
 - For immunocompromised, (HIV and CD4 < 200 cells/mm3, or after transplant),→ Interferon- gamma release assay and a concurrent Mantoux test:
 - ❖ If either test is positive → assess for active TB.
 - ❖ If assess for active TB is negative, → treatment for latent TB infection.
 - - Quantaferon testing is not influenced by BCG vaccination status
 - A positive test would, therefore, indicate prior exposure to M. tuberculosis (active or latent TB)
 - - The main disadvantage of the IGRA is its inability to distinguish between active and latent TB.
- Chest x-ray
 - ⇒ **NO** TB-related findings on chest x-ray (e.g., hilar lymphadenopathy, upper lobe opacification, or cavitation),

Treatment (NICE guidelines 2016)

- Treatment of LTBI can reduce the risk of development of disease by 90%
- For adults between the ages of 35 and 65 years, offer drug treatments only if hepatotoxicity is not a concern.
- test for hepatitis B, C and HIV before starting treatment for latent TB.
- NICE now give two choices for treating latent tuberculosis:
 - ⇒ 3 months of isoniazid (with pyridoxine) and rifampicin
 - For people younger than 35 years if hepatotoxicity is a concern after an assessment of both liver function (including transaminase levels) and risk factors.
 - ⇒ 6 months of isoniazid (with pyridoxine)
 - if interactions with rifampicin are a concern, for example, in people with HIV or who have had a transplant.

NICE advises that once a diagnosis of pulmonary TB has been made then **close contacts** should be managed as follow:

- If asymptomatic and younger than 65 years, then:
 - ⇒ test for latent TB.
 - If Mantoux-negative and unvaccinated then offer vaccination.
 - If at risk of HIV then test for HIV first (HIV testing and if negative, then BCG vaccination).
- If asymptomatic and older than 65 years then assess with a chest X-ray.

Miliary TB

Overview

miliary TB most likely occur in young children.

Features

- presents with a gradual onset of vague ill health, loss of weight and then fever.
- TB meningitis
 - ⇒ 15 20% of patients who have miliary TB also have TB meningitis at the time of presentation.
 - ⇒ 33% of patient with TB meningitis have concomitant miliary TB.
- Hepatosplenomegaly is seen in advanced disease.
- · Choroidal tubercles can be seen in the eyes.

Investigations

- · tuberculin test is often negative.
 - ⇒ negative in up to half of patients with severe disease
- chest x ray
 - ⇒ may be normal in up to one third of patients.
 - ⇒ The classic millet seed nodules are small measuring about 1-2 mm.
- Not all patients will be sputum positive and with evidence supporting a diagnosis of tuberculosis treatment should be commenced swiftly.
- Transbronchial biopsy positive at an early stage.
- Biopsy of liver and bone marrow might be required.



Milliay TB

Non-tuberculous mycobacterial infections

Opportunistic mycobacteria

- Mycobacterium kansasii
- Mycobacterium malmoense
- Mycobacterium xenopi
- Mycobacterium avium intracellular(The presence of acid fast bacilli (AFB) and absence of TB (Mycobacterium tuberculosis negative on culture.) suggests an atypical AFB such as M. avium.)
 - ⇒ The presence of AFB yet absence of TB suggests an atypical AFB such as *M. avium*.
 - Mycobacterium avium causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm³.

Mycobacterium malmoense

- is a non-tuberculous mycobacterium
- most commonly causes pulmonary infection in middle-aged and older adults with pre-existing lung disease or immunodeficiency and can also cause local invasion from a skin lesion.
- It causes nonspecific symptoms, such as malaise and weight loss, or chest symptoms that take an atypical course.

Pathophysiology

- they can colonise structurally abnormal lung, for example in patients with:
 - ⇒ Cavitary disease
 - ⇒ Bronchiectasis
 - ⇒ Chronic obstructive pulmonary disease
 - ⇒ Such patients might not always require treatment. However, if treatment is required, then it is usually for longer than the standard 6 months needed to treat pulmonary tuberculosis
- 'atypical' mycobacteria differ from *M. tuberculosis* in that they are ubiquitous organisms and have no person-to-person spread.
- Mycobacterium marinum infection
 - ⇒ It is an uncommon atypical mycobacterium infection
 - ⇒ The skin is the most common site of infection, where it usually produces a solitary indolent granulomatous lesion the 'fish tank granuloma'.
 - ⇒ usually seen in **patients who handle fish** or swim in freshwater or saltwater.
 - ⇒ occurs when contaminated water is exposed to skin that has experienced open trauma.



fish tank granuloma' caused by Mycobacterium marinum

Diagnosis

- A single isolate from a non-sterile site might not be significant and can just represent contamination. More than two isolates from a non-sterile site are required to establish disease.
- Chest X-ray => (like other mycobacterium) upper-zone fibrosis and cavitation.

Treatment

No need to isolate patients or notify public health authorities.

Multidrug-resistant tuberculosis (MDR-TB).

Definition

- Defined as resistance to rifampicin and isoniazid, with or without resistance to other anti-TB drugs.
- defined as positive cultures after 4 months of therapy.

Epidemiology

- Rare in previously untreated white patients born in the UK(< 2%).
- Higher levels of resistance occur in Indian subcontinent and black, with isoniazid resistance occurring in 4-6% of such patients.

Risk factors

- Poor compliance (the most common reason)
- Previous anti-TB treatment
- Contact with a known case of drug-resistant TB
- Birth in a foreign country, particularly high-incidence countries
- HIV infection
- Residence in London
- Age profile, with highest rates between ages 25 and 44
- Male gender
- Homelessness
- Intravenous drug use
- Infection acquired in institutions (eg prison)

Treatment

- Directly observed therapy is recommended
- should be treated with an injectable agent such as amikacin, kanamycin or capreomycin, in combination with a fluoroquinolone and at least three other agents. At least 5 drugs, one of which is a quinolone, is the recommended
- Ideally the <u>injectable</u> agent is administered daily for the first <u>6-8 months</u>, forming an intensive phase of treatment, with other drugs then continued for a total of **18-24 months**.
- In practice, unwanted effects may lead to intravenous therapy being discontinued early.

Leprosy

Definition

• Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*.

Features

- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- · sensory loss

Types

- The degree of cell mediated immunity determines the type of leprosy a patient will develop:
 - ⇒ Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')
 - extensive skin involvement
 - symmetrical nerve involvement
 - ⇒ High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')
 - limited skin disease
 - asymmetric nerve involvement

Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine
- BNF advice:
 - ⇒ multibacillary leprosy (>6 lesions) → rifampicin, dapsone and clofazimine for 12 months.
 - ⇒ paucibacillary leprosy (5 or less lesions) → rifampicin and dapsone for 6 months.

Vaccinations

Live attenuated vaccines

- BCG
- measles, mumps, rubella (MMR)
- oral polio
- oral rotavirus
- oral typhoid

- influenza (intranasal)
- yellow fever
- Varicella

Live attenuated vaccines are contraindicated in all HIV positive and immunocompromised patients.

Inactivated preparations

- rabies
- influenza (intramuscular)

Detoxified exotoxins

tetanus

Extracts of the organism/virus (sometimes termed fragment) (may also be produced using recombinant DNA technology)

- diphtheria
- pertussis ('acellular' vaccine)
- hepatitis B
- · meningococcus, pneumococcus, haemophilus

Notes

- influenza:
 - ⇒ different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly haemagglutinin and neuraminidase)
- cholera:
 - contains inactivated Inaba and Ogawa strains of Vibrio cholerae together with recombinant B-subunit of the cholera toxin
- hepatitis B:
 - ⇒ contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology

Contraindications to pertussis immunisation

- · Acute illness until recovered
- Previous reaction to pertussis:
 - Local: an extensive area of redness and swelling which becomes indurated, involving most of the anterolateral surface of the thigh or a major part of the circumference of the upper arm
 - 2. **General: fever equal to or more than 39.5°C within 48 hours of vaccine**, anaphylaxis, bronchospasm, laryngeal oedema, generalised collapse, prolonged hyporesponsiveness, prolonged inconsolable or high-pitched screaming of more than four hours, convulsions or encephalopathy occurring within 72 hours.

Splenectomised patients

- Splenectomised patients are at increased risk of infection with:
 - ⇒ encapsulated bacteria
 - A popular mnemonic to remember most of the encapsulated bacteria is the SHINE SKIS bacteria (S. pneumo, Hib, N. meningitidis, E. Coli, Salmonella, Klebsiella, Group B Strep).
 - infections that are filtered by the spleen (for example, malaria).
- When <u>elective splenectomy</u> is planned, vaccines to pneumococcus and meningiococcus should be given **two weeks pre-surgery** to allow an antibody response to evolve.
- Patients who have <u>emergency splenectomies</u> should be vaccinated post-operatively (most effective if performed at least 14 days after surgery)

Prophylaxis in splenectomy

- Following a splenectomy patients are particularly at risk from pneumococcus, Haemophilus, meningococcus and (Capnocytophaga canimorsus infections usually from dog bites)
- Vaccination
 - ⇒ if elective, should be done 2 weeks prior to operation
 - ⇒ Hib, meningitis A & C
 - ⇒ annual influenza vaccination
 - ⇒ pneumococcal vaccine every 5 years
- Antibiotic prophylaxis
 - penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

MRCPUK-part-1-January 2018 exam: H/O emergency splenectomy. Following this he takes penicillin V on a daily basis. He is unsure of his vaccination history. Which organism is he particularly suscepitble to?

→ Haemophilus influenza (Penicillin V would protect him against Streptococcus pneumoniae but notHaemophilus influenzae due to the production of beta-lactamases by the organism)

MRCPUK-part-1-September 2019 exam: A 12-year-old boy who had a splenectomy following RTA, he had his full immunisation course as a child and was given a repeat pneumococcal vaccination 5 days following surgery. What is the most appropriate ongoing management?

→ Booster dose of Hib and MenC vaccine + annual influenza vaccination + lifelong penicillin V

Post-exposure prophylaxis

Post-exposure prophylaxis for HIV: oral antiretroviral therapy for 4 weeks

Hepatitis A

 Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation

Hepatitis B

- HBsAg positive source:
 - ⇒ if the person exposed is a known responder to HBV vaccine then a booster dose should be given.
 - ⇒ If they are in the process of being vaccinated or are a non-responder they need to have hepatitis B immune globulin (HBIG) and the vaccine
- unknown source:
 - ⇒ for known responders the green book advises considering a booster dose of HBV vaccine.
 - ⇒ For known non-responders → HBIG + vaccine should be given
 - ⇒ those in the process of being vaccinated should have an accelerated course of HBV vaccine.
 - ⇒ <u>accelerated course of HBV vaccine</u> → given at zero, one and two months. For those who are at continued risk, a fourth dose is recommended at 12 months.

	Source person		
Exposed person	HBsAg positive	unknown	
responder to HBV vaccine	booster HBV vaccine	booster HBV vaccine	
non-responder	(HBIG) + vaccine	HBIG + vaccine	
in the process of vaccination	(HBIG) + vaccine	accelerated course of HBV vaccine (given at zero, one and two months)	

Hepatitis C

Monthly PCR - if seroconversion then interferon +/- ribavirin

HIV

- Three antiretroviral agents for 1 month
 - New guidelines in 2014 recommend three-agent PEP with <u>Truvada®</u> (tenofovir and emtricitabine) and raltegravir, which should both be taken for 1 month.
 - ⇒ (i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- Serological testing at 12 weeks following completion of post-exposure prophylaxis
- Reduces risk of transmission by 80%

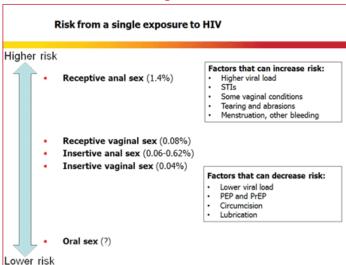
Varicella zoster

• VZIG for IgG negative pregnant women/immunosuppressed

Estimates of transmission risk for single needle stick injury

Hepatitis B	20-30%
Hepatitis C	0.5-2%
HIV	0.3%

First line management of needle stick injuries includes immediate washing of the affected area under running water.



UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE)

- If the source is of unknown status: → establish the HIV status of the source.
- Source individual known to be HIV-positive:
 → determine the HIV viral load, resistance profile and treatment history.
- if the source is on antiretroviral therapy (ART) with a confirmed and sustained (>6 months) undetectable plasma HIV viral load → PEPSE is no longer recommended

- ⇒ However, if there are any doubts about the HIV viral load history or the source's adherence to ART → PEP should be given following unprotected receptive anal intercourse.
- ⇒ Initiation of PEPSE is recommended as soon as possible after exposure, preferably within 24 hours of exposure but can be offered up to 72 hours.
- ⇒ The first-line regimen is Truvada and raltegravir
 - Truvada → fixed-dose combination of two antiretroviral medications: tenofovir disoproxil and emtricitabine (both are Nucleoside analog reverse-transcriptase inhibitors (NRTIs)
 - Raltegravir (<u>integrase inhibitors</u>, a new class of HIV drugs) targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV.
- ⇒ PEPSE beyond 72 hours are not recommend
- ⇒ duration of PEPSE should be 28 days
- ⇒ follow-up HIV testing at 8-12 weeks after exposure
- ⇒ pregnancy should not alter the decision to start PEPSE. Women must be counselled that antiretroviral agents used for PEPSE are unlicensed in pregnancy and risks / benefits must be carefully discussed
- ⇒ In the event of a further high-risk sexual exposure in the last two days of the PEPSE course the PEP should be continued for 48 hours after the last high-risk exposure
- ⇒ If the recipient has missed more than 48 hours of PEPSE then the course should be discontinued.

Brucellosis

Overview

- Brucellosis is a zoonosis more common in the Middle East and in farmers.
- · Gram negative bacilli
- It is considered a class B bioterrorist agent, is easily spread by aerosol, and is a significant hazard in microbiology laboratories.
- Four major species cause infection in humans: B melitensis (sheep), B abortus (cattle), B canis and B suis (pigs).
- incubation period 2 6 weeks
- Most cases of brucellosis in Northern Europe and North America are acquired overseas and/or from consuming unpasteurised milk products, including cheese.

Features

- non-specific:
 - ⇒ fever, (prolonged fever of unknown origin)
 - ⇒ malaise
- hepatosplenomegaly
- sacroilitis: spinal tenderness may be seen. Brucellosis is a recognised cause of spondylitis
 - ⇒ associated rheumatic features in about 50% of cases.
- · complications: osteomyelitis, infective endocarditis, meningoencephalitis, orchitis
- leukopenia is common

Diagnosis

- the Rose Bengal plate test can be used for screening but other tests are required to confirm the diagnosis
- Brucella serology is the best test for diagnosis
- blood and bone marrow cultures may be suitable in certain patients, but these tests are
 often negative

⇒ 75% have a positive blood culture (90% of bone marrow cultures will be positive).

Management

doxycycline and streptomycin

Cat scratch disease (CSD)

Cat scratch disease - caused by Bartonella henselae

Definition: a benign, self-limiting infectious disease that is transmitted mainly by cats (via scratching, biting, or licking)

Pathogen: Gram negative rod Bartonella henselae

Features

- · fever, headache, malaise
- history of a cat scratch
- · regional lymphadenopathy
- In Immunocompromised individuals (e.g., patients with HIV) → Bacillary angiomatosis
 (vascular proliferation, which leads to the development of solitary or multiple, red-purple
 papules that bleed easily).

Treatment

- Mild or moderate cases: azithromycin (5-day course) to decrease lymphadenopathy and the duration of illness
- In the case of persistent and/or disseminated disease (e.g., bacillary angiomatosis): erythromycin OR doxycycline
- In the case of CNS involvement or endocarditis: rifampicin PLUS either erythromycin OR doxycycline

Whooping cough (pertussis)

Bacteria

- caused by the bacterium Bordetella pertussis.
- gram-negative aerobic coccobacillus
 - ⇒ The virulence factors of Bordetella pertussis include its eponymous toxin and tracheal cytotoxin.
- grows best on Bordet-Gengou agar and Regan-Lowe medium (Bordet for Bordetella)

Epidemiology

• now more common in adolescents and adults than in children.

Mechanism

- The tracheal cytotoxin from Bordetella pertussis kills ciliated cells along the respiratory epithelium.
- Pertussis toxin inactivates Gi, an inhibitory protein. Gi normally inhibits activation of adenylate cyclase. Therefore, the pertussis toxin inhibits an inhibitor leading to increased activity of adenylate cyclase.
 - ⇒ Pertussis toxin → \(\) Gi → \(\) adenylate cyclase

Features

- Pertussis has three major phases: the catarrhal phase (like the common cold), the paroxysmal phase (bouts of coughing), and the convalescent phase (resolution).
- Lymphocytosis is typically found.
 - ⇒ it causes a profound leucocytosis by inhibiting chemokines that normally remove white cells from the blood stream.

Complications

- pneumonia, seizures, and encephalopathy
- A rare complication is a hemiseizure-hemiplegia syndrome, which is thought to be related to post-immunisation hyperthermia rather than direct neurological toxicity.

Treatment

- Treatment is largely supportive, but antibiotics can reduce the duration of symptoms.
- Erythromycin, clarithromycin and azithromycin are first choice

Prevention

 The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussistetanus (DPT) shot

Acute epiglottitis

Overview

- Acute epiglottitis is rare but serious infection caused by Haemophilus influenzae type B.
- Prompt recognition and treatment is essential as airway obstruction may develop.
- Epiglottitis was generally considered a disease of childhood but in the UK it is now more common in adults due to the immunisation programme.
- The incidence of epiglottitis has decreased since the introduction of the Hib vaccine

Features

- Rapid onset
- High temperature, generally unwell
- Stridor
- Drooling of saliva (the most specific sign)

Diagnosis

- the preferred method of diagnosis → direct visualization of the epiglottis using nasopharyngoscopy/laryngoscopy → cherry-red epiglottis
 - ⇒ No attempt should be made to visualise the epiglottis until an anaesthetist is present as there is a high risk of causing acute airway obstruction by touching the inflamed tissue.
- Lateral neck soft-tissue radiography
 - ⇒ useful screening tool in suspected stable patient.
 - ⇒ Only 79% of epiglottis cases are diagnosed by neck soft-tissue radiographs
 - ⇒ The classic findings are:
 - swollen epiglottis (ie, a thumb sign),
 - thickened aryepiglottic folds, and
 - obliteration of the vallecula (pre-epiglottic space). (vallecula sign).
 - The vallecula is the air pocket found at the level of the hyoid bone just anterior to the epiglottis.
- blood culture

Differential

- · cough is specific for croup
- drooling is specific for epiglottitis
- laryngomalacia improves in the prone position

Treatment

- Unstable patients → immediate airway management. Early intubation is essential, especially in cases where there is respiratory distress.
- Third generation cephalosporin is the treatment of choice.
- Close contacts of patients in whom Haemophilus influenzae type b is isolated should receive rifampin prophylaxis (20 mg/kg; not to exceed 600 mg/d for 4 d).

 Recurrent episodes of acute epiglottitis in adults is unusual and, when present, warrants immune system investigation.

Haemophilus influenzae requires hemin (factor X) and NAD+ (factor V) for growth. Other Haemophilus species require only NAD+ and therefore grow on blood agar. Haemophilus influenzae: culture requirements:

→ Read Hemophilus as "HemoFive": · Needs Heme with Factors Five and Ten.

Cellulitis

Cellulitis

- Staphylococcus aureus and Streptococci are the commonest causative organisms.
- Group B Streptococcus has a predilection for diabetic patients

Definition

inflammation of the skin and subcutaneous tissues.

Causes

- Staphylococcus aureus and Streptococci are the commonest causative organisms.
- Group B Streptococcus has a predilection for diabetic patients and is the likeliest causative organism in diabetics

Features

- · commonly occurs on the shins
- · erythema, pain, swelling
- systemic upset such as fever
- Cellulitis **does not** have sharp, well-defined borders, unlike an erysipelas infection.

Eron classification

NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis:

Class	Features
I	There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities
II	The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection
Ш	The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromise
IV	The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis

Management

- Criteria for admission for intravenous antibiotics
 - ⇒ Eron Class III or Class IV cellulitis.
 - ⇒ severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
 - ⇒ very young (under 1 year of age) or frail.
 - ⇒ immunocompromised.
 - ⇒ significant lymphoedema.

- ⇒ facial cellulitis (unless very mild) or periorbital cellulitis.
- Management Eron Class II cellulitis:
 - Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person.
- Other patients can be treated with oral antibiotics.
- Antibiotics
 - ⇒ mild/moderate cellulitis
 - First line → flucloxacillin (BNF recommendation)
 - first choice to treat sensitive staphylococcal infections
 - MRSA is resistant to flucloxacillin.
 - in patients allergic to penicillin → Clarithromycin or clindamycin.
 - in patients who have failed to respond to flucloxacillin → oral clindamycin
 - The most appropriate treatment is clindamycin and flucloxacillin, which covers the majority of organisms responsible for cellulitis.
 - ➡ Flucloxacillin is bactericidal for both Staphylococcus and Streptococcus, whereas clindamycin has an anti-toxin effect for both these groups of organisms (in addition to Clostridium perfringen). Their effect is therefore synergistic, and they should be used together where rapid control is required (e.g. in finger cellulitis) or in severe cases
 - Although clindamycin is a <u>bacteriostatic</u> antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of toxic shock syndrome (TSS).
 - If no significant improvement within 48 hours, the patient should be readmitted for intravenous antibiotics.
 - ⇒ Severe cellulitis
 - should be treated with intravenous benzylpenicillin + flucloxacillin.
 - If there is any suspicion of tendon involvement (Intact joint movements make this less likely) → the plastics or orthopaedics team should be asked to review and intravenous antibiotics initiated.

Methicillin-resistant Staphylococcus aureus (MRSA)

Epidemiology

• In many hospitals, 40%-50% of the S. aureus isolates are resistant to methicillin

Mechanism of resistance

- Penicillin binding proteins are the characteristic mutated proteins in methicillinresistant Staphylococcus aureus.
- The resistant organisms produce penicillin-binding proteins (PBPs) that have a low affinity
 for binding beta-lactamase antibiotics (Modification of target penicillin-binding
 proteins). Other organisms which do the same are Pneumococci and Enterococci.

Who should be screened for MRSA?

- · all patients awaiting elective admissions
 - ⇒ exceptions include:
 - terminations of pregnancy
 - ophthalmic surgery
 - Patients admitted to mental health trusts.
- all emergency admissions.

Where is the site of most concern for staff carriage of MRSA?

• The nose is the area of carriage for MRSA which gives most area for concern with respect to carriage by staff.

How should a patient be screened for MRSA?

- nasal swab and skin lesions or wounds
 - ⇒ the swab should be wiped around the inside rim of a patient's nose for 5 seconds
 - ⇒ the microbiology form must be labelled 'MRSA screen'

Suppression of MRSA from a carrier once identified

- nose:
 - ⇒ mupirocin 2% in white soft paraffin, TDS for 5 days
- skin:
 - ⇒ chlorhexidine gluconate, OD for 5 days.
 - Apply all over but particularly to the axilla, groin and perineum

Treatment of MRSA infections

- Vancomycin → the first line
- Teicoplanin
- Linezolid
 - ⇒ Linezolid is the only oral medication available against MRSA.
- Ceftaroline
 - ⇒ fifth generation cephalosporin
 - ⇒ Ceftaroline is the only cephalosporin to cover MRSA.
- Some strains may be sensitive to the antibiotics listed below but they <u>should not generally</u> be used alone because resistance may develop:
 - ⇒ rifampicin
 - ⇒ macrolides
 - ⇒ tetracyclines
 - ⇒ aminoglycosides
 - ⇒ clindamycin
- Relatively new antibiotics such as linezolid, <u>quinupristin /dalfopristin combinations</u> and tigecycline have activity against MRSA but should be reserved for resistant cases

MRCPUK-part-1-January-2009: What is the most effective single step to reduce the incidence of MRSA?

→ Hand hygiene

MRCPI-part-1-jan-2017: What is the most appropriate antibiotic regimen for possible line sepsis from an indwelling permacath?

Vancomycin + Gentamicin

The antibiotic chosen should have both gram-positive and gram-negative cover, including MRSA. vancomycin and doxycycline are able to treat MRSA, but doxycycline has limited gram-negative cover, unlike gentamicin.

Necrotising fasciitis

Overview

Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages.

Classification (according to the causative organism):

- Type 1 is caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics)
- Type 2 is caused by Streptococcus pyogenes
 - ⇒ commonly caused by group A Streptococci

Features

- acute onset
- · painful, erythematous lesions
- · extremely tender over infected tissue

Management

- · urgent surgical referral debridement
- intravenous antibiotics
 - ⇒ Clindamycin and Tazocin
 - Clindamycin
 - bacteriostatic
 - ❖ inhibits formation of peptides bonds at 50S ribosomal subunit
 - It is also a potent suppressor of bacterial toxin synthesis.
 - Group A Streptocooci are usually very sensitive to benzylpenicillin so this is frequently added though this does not neutralises the toxin.

Toxic shock syndrome (TSS)

Staphylococcus aureus → Toxic shock syndrome toxin → binds to major histocompatibility complex <u>II</u> and T cell receptor → overwhelming release of cytokines → shock.

Causes

- Staphylococcus aureus, which releases enterotoxin type B (i.e. toxic shock syndrome toxin-1),
- Streptococcus pyogenes, which releases pyogenic exotoxins.

Risk factors

- Recent menstruation
 - ⇒ Although the earliest described cases involved mostly menstruating women using highly absorbent tampons, only 55% of current cases are associated with menstruation.
- Recent use of barrier contraceptives such as diaphragms and vaginal sponges
- Vaginal tampon use (especially prolonged)
- Recent childbirth
- · Recent surgery,
- · Current S. aureus infection.

Features

- non-specific (e.g., fever, chills, myalgias, headache),
- toxicity occurs early, resulting in serious life-threatening disease
- Staphylococcal scalded skin syndrome
 - ⇒ Diffuse erythema that desquamates as the patient recovers
 - ⇒ Occur 10% of patients
 - ⇒ Exotoxin A is the causative toxin in staphylococcus scalded skin syndrome.
 - ⇒ most common in children but can be seen in immunocompromised adults.
 - destroys keratinocyte attachments in the stratum granulosum, leading to a very superficial sloughing of the epidermis that heals completely.
 - ⇒ It is also known as Pemphigus neonatorum or Ritter disease.
- multi-organ system failure.

Types

- Streptococcal toxic shock syndrome (TSS) can occur with infection at any site but is more commonly associated with an infected cutaneous site.
- Staphylococcal TSS (menstrual or non-menstrual)
 - ⇒ severe systemic reaction to staphylococcal exotoxins.
 - ⇒ associated with extended tampon use, postpartum infections, and other sites of infection with the organism.

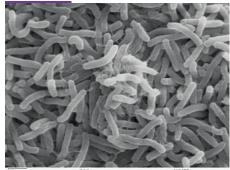
Diagnosis

- Centers for Disease Control and Prevention diagnostic criteria
 - ⇒ fever: temperature > 38.9 C
 - ⇒ hypotension: systolic blood pressure < 90 mmHg
 - ⇒ diffuse erythematous rash
 - ⇒ desquamation of rash, especially of the palms and soles
 - ⇒ involvement of three or more organ systems: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion)

Treatment

- supportive care in an ICU,
- early empirical antibiotic treatment, and further culture-sensitive antibiotic treatment.
 - ➡ Although clindamycin is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of TSS.
- Surgical debridement may be needed for deep-seated streptococcal infections.

Cholera



electron microscope image of Vibrio cholerae bacteria

Overview

- caused by Vibro cholerae Gram negative bacteria
- Because the organism is not acid-resistant, it depends on its large inoculum size (infectious dose) to withstand gastric acidity.
 - ⇒ If ingested with water, a higher infectious dose is needed. When ingested with food, fewer organisms are required to produce disease.
 - ⇒ ↓ gastric acidity (anti-acid drugs, gastrectomy) → ↑risk of cholera infection and severity

Mechanism by which cholera leads to fluid loss:

• Cholera toxin has two parts, A and B.

- ⇒ B subunits are responsible for binding to a ganglioside (monosialosyl ganglioside, GM1 receptor) located on the surface of the cells that line the intestinal mucosa.
- ⇒ B binds while A activates G protein → activates adenylate cyclase →
 ↑(cAMP) → unrestricted chloride secretion from villous crypts.

cholera toxin stimulates the generation of cyclic AMP as the second messenger

Features

- · profuse 'rice water' diarrhoea
- · dehydration
- hypoglycaemia
 - After dehydration, hypoglycemia is the most common lethal complication of cholera in children.

Management

- oral rehydration therapy
- · antibiotics: doxycycline, ciprofloxacin

Congenital infections

Congenital rubella

- sensorineural deafness
- congenital cataracts

The major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus

Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic

	Rubella	Toxoplasmosis	Cytomegalovirus
Characteristic features	 Sensorineural deafness Congenital cataracts Congenital heart disease (e.g. patent ductus arteriosus) Glaucoma 	Cerebral calcificationChorioretinitisHydrocephalus	Growth retardationPurpuric skin lesions
Other features	 Growth retardation Hepatosplenomegaly Purpuric skin lesions 'Salt and pepper' chorioretinitis Microphthalmia Cerebral palsy 	AnaemiaHepatosplenomegalyCerebral palsy	 Sensorineural deafness Encephalitis/seizures Pneumonitis Hepatosplenomegaly Anaemia Jaundice Cerebral palsy

Chickenpox (Varicella-zoster virus)

Overview

- Chickenpox is caused by primary infection with varicella zoster virus.
- Shingles is reactivation of dormant virus in dorsal root ganglion
- Chickenpox is highly infectious (infection rate in household contacts of 90%).
- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared*
- incubation period = 10-21 days
- It is commonest in spring time
- Causes congenital limb deformity
- HIV
 - ⇒ HIV-positive patients are more prone to herpes zoster regardless of their CD4 count.
 - ⇒ In addition to the typical dermatomal distribution of the vesicular rash, HIV patients occasionally have vesicles scattered in adjacent dermatomes.
 - ⇒ In advanced HIV disease VZV can manifest as severe disseminated disease.

Clinical features (tend to be more severe in older children/adults)

- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management is supportive

- · keep cool, trim nails
- calamine lotion
- school exclusion: current HPA advice is 5 days from start of skin eruption. They also state
 'Traditionally children have been excluded until all lesions are crusted. However,
 transmission has never been reported beyond the fifth day of the rash.'
- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered
 - Aciclovir (also famciclovir, and ganciclovir) acts through inhibition of viral (DNA) polymerase but it is a pro-drug and first requires phosphorylation by thymidine kinase.
 - Resistance arises when the virus lacks thymidine kinase
 - ⇒ For thymidine kinase-deficient varicella-zoster virus strain:
 - <u>Cidofovir</u> does not require activation by viral thymidine kinase; therefore, it would be best suited to treat the thymidine kinase-deficient varicella-zoster virus.
- adults chicken pox should be treated with acyclovir within 24 hours of the appearance of rash because it can lessen the occurrence of post herpetic neuralgia.

Complications

- Common complication is secondary bacterial infection of the lesions.
- Chicken pox in the first and second trimester can produce a syndrome of skin scarring, hypoplastic limbs, eye and central nervous system impairments.
- · Rare complications include
 - ⇒ Varicella pneumonia
 - Varicella pneumonia occurs in up to 20% of adults with chickenpox,
 - uncommon in children

- The risk is higher in smokers and pregnancy.
- Features
 - appearing three to five days into the course of the illness.
 - Symptoms include tachypnoea, cough, dyspnoea, and fever.
 - Cyanosis, pleuritic chest pain and haemoptysis are common.
- Treatment → Aciclovir
- ⇒ Encephalitis (cerebellar involvement may be seen)
- ⇒ Disseminated haemorrhagic chickenpox
- ⇒ Arthritis, nephritis and pancreatitis may very rarely be seen

mechanism of acyclovir resistance → reduced production of viral thymidine kinase



Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

Chickenpox exposure in pregnancy

Chickenpox exposure in pregnancy - first step is to check antibodies

 In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Risks to the fetus and neonate relate to the time of infection:

. Less than 20 weeks pregnancy:

^{*}it was traditionally taught that patients were infective until all lesions had scabbed over

- ⇒ congenital varicella (limb hypoplasia, microcephaly, cataracts, growth retardation, skin scarring). High mortality.
- ⇒ The incidence of congenital varicella syndrome is about 2% in mothers who develop primary chickenpox in the first half of the pregnancy.
- Second to third trimester:
 - ⇒ herpes zoster in an otherwise healthy infant.
- Minus seven days to plus seven days after delivery:
 - ⇒ severe and even fatal disease (30% mortality).

Risks to the mother

• 5 times greater risk of pneumonitis

Fetal varicella syndrome (FVS)

- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

Other risks to the fetus

- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester
- severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

Management of chickenpox exposure

- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently checked for varicella antibodies
- if the pregnant women is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure
- consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

Varicella zoster immunoglobulin (VZIG)

- prepared from pooled plasma of UK blood donors with a history of recent chickenpox or herpes zoster.
- Donors are screened for HIV, hepatitis B and hepatitis C.
- VZIG prophylaxis is recommended for patients who fulfil all the following criteria:
 - 1. A clinical condition that increases the risk of severe varicella, (for example, immunosuppression, neonates, **pregnant women**)
 - 2. No antibodies to varicella zoster
 - 3. Significant exposure to chickenpox or herpes.
- VZIG prophylaxis is of no benefit if chickenpox has already developed.
- Severe or fatal varicella can occur despite VZIG prophylaxis. Active immunisation should therefore be used for susceptible immunosuppressed patients at long term risk.

Cytomegalovirus

Overview

- Cytomegalovirus (CMV, HHV-5), is one of the herpes viruses.
- Herpes viridae is the family of viruses to which cytomegalovirus belongs.
- Double stranded DNA virus.
- Mononuclear cells are the class of leukocytes in which cytomegalovirus lies dormant.
- It is thought that around 50% of people have been exposed to the CMV virus although it only usually causes disease in the immunocompromised, for example people with HIV or those on immunosuppressants following organ transplantation.

Diagnosis

infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies

Patterns of disease

- Congenital CMV infection
 - features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitis (seizures) and hepatosplenomegaly
- CMV mononucleosis
 - ⇒ infectious mononucleosis-like illness
 - ⇒ may develop in immunocompetent individuals
- CMV retinitis
 - ⇒ common in HIV patients with a low CD4 count (< 50)
 - ⇒ presents with visual impairment e.g. 'blurred vision'. Fundoscopy shows retinal haemorrhages and necrosis, often called 'pizza' retina
 - ⇒ IV ganciclovir is the treatment of choice
 - Valganciclovir is an oral pro-drug for ganciclovir, with similar bioavailability but without the need to deliver it IV, making it the preferred option here.
 - The efficacy of valganciclovir is similar to ganciclovir without the need for IV administration, and this drives ganciclovir as the option where oral therapy isn't tolerated.
 - The toxicity profile for valganciclovir is the same as that for ganciclovir, with bone marrow suppression the main concern.
 - ⇒ Foscarnet is the drug of choice for ganciclovir-resistant cytomegalovirus retinitis.
- CMV encephalopathy: seen in patients with HIV who have low CD4 counts
- CMV pneumonitis
- CMV colitis
 - ⇒ HIV+ bloody diarrhea+ no abdominal pain +normal stool examination → Do Colonoscopy to diagnose CMV colitis
 - ⇒ Patients with inflammatory bowel disease are at increased risk of CMV colitis particularly those on immunosuppression.
 - ⇒ COLONOSCOPY finding → multiple ulcer and mucosal erosion
 - ⇒ The most appropriate investigation is → Flexible sigmoidoscopy and biopsy
 - in severe colitis endoscopy should be limited to flexible sigmoidoscopy only due to an increased risk of perforation.
 - Biopsy shows: cytomegalic cell+ intranuclear inclusion body

Dengue fever

Definition

 Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

Pathogen

- · caused by Dengue virus, RNA virus of the genus Flavivirus
- Transmitted by the Aedes aegyti mosquito
- Incubation period 4-10 days.
 - ⇒ If symptoms appear more than 2 weeks after returning from a dengue-endemic region, it is very unlikely that dengue is the cause.

Epidemiology

- Distribution: tropical regions worldwide, particularly Asia (e.g., Thailand)
- Most common viral disease affecting tourists in tropical regions

Features

- · headache (often retro-orbital)
- fever
- myalgia (severe musculoskeletal pain is a prominent feature) hence the name breakbone fever.
- · pleuritic pain
- facial flushing (dengue)
- maculopapular rash (confluent erythematous rash over the precordium)
 - ⇒ When the patient is near recovery there may develop a maculopapular rash beginning on the trunk and spreading to the extremities and the face.
- There is often adenopathy, palatal vesicles and sclera injection on the first day.
- Epistaxis and scattered petechiae may be observed.

Complication

 a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

Laboratory tests

- Leukopenia
- Neutropenia
- Thrombocytopenia
- ↑ AST
- Hct significantly increased or decreased in DHF (due to plasma leakage)

Diagnosis

• diagnosed by dengue fever serology.

Treatment

• symptomatic e.g. fluid resuscitation, blood transfusion etc

Herpes simplex virus

Pathogen

- Herpes simplex virus is a DNA virus.
- There are two strains of the herpes simplex virus (HSV) in humans:
 - 1. HSV-1 → most commonly cause orofacial disease
 - 2. HSV-2 → most commonly cause genital disease.
- Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap
- Worldwide seroprevalence is high, with antibodies detectable in over 90% of the population.
 - ⇒ Of these cases, approx. 60% are caused by HSV-1.
- Incubation period → 2 days to 2 weeks.

Pathophysiology

- Inoculation: The virus enters the body through mucosal surfaces or small dermal lesions.
- Neurovirulence: The virus invades, spreads, and replicates in nerve cells.
- Latency: After primary infection, the virus remains dormant in the ganglion neurons.
 - ⇒ Trigeminal ganglion: HSV-1
 - ⇒ Sacral ganglion: HSV-2
- Reactivation: triggered by various factors (e.g., immunodeficiency, stress, trauma) →
 clinical manifestations
- Dissemination
 - ⇒ Infection spreads to unusual sites (e.g., lungs, gastrointestinal tract, eyes)
 - ⇒ May occur in pregnant patients or patients with severe immunodeficiency
- Recurrent attacks tend to be shorter and less severe.

Transmission

- Only from direct contact with mucosal tissue or secretions of another infected person
- Because the virus dies quickly outside of the body, it's nearly impossible to get the infection through contact with toilets, towels or other objects used by an infected person
- Infection with HSV-1 usually is acquired in childhood via saliva.
- HSV-2 is mostly spread through genital contact

Features

Herpes zoster usually has a prodrome pain before the vesicles appear. It usually follows a particular dermatome but in immune suppression the disease may affect more than one dermatome.

Herpes simplex II is the wrong answer. Herpes simplex II vesicles may appear, but they never follow a particular dermatome.

- Up to 80% of herpes simplex infections are asymptomatic.
- · Labial herpes (herpes labialis)
 - ⇒ Pathogen → Mostly HSV-1
 - ⇒ Recurring, erythematous vesicles that turn into painful ulcerations, also known as cold sores; oral mucosa and lip borders
 - ⇒ In orofacial HSV infections, the **trigeminal ganglia** are most commonly involved
- Herpetic gingivostomatitis
 - ⇒ Mainly in children (~ 1–6 years), but also immunocompromised patients

- ⇒ Erythema and painful ulcerations on perioral skin and oral mucosa
- Genital herpes (herpes genitalis) → painful genital ulceration
 - \Rightarrow Pathogen \rightarrow HSV-2
 - ⇒ Blistering and ulceration of the external genitalia or perianal region (cervix/rectum) → "punched-out" ulcer
 - ⇒ Painful lymphadenopathy in the groin area (tender inguinal lymphadenitis, usually bilateral.)
 - ⇒ In genital HSV infection, the sacral nerve root ganglia (S2-S5) are involved.

Eczema herpeticum

- ⇒ associated with preexisting skin conditions, most often atopic dermatitis
- ⇒ Fever, malaise, lymphadenopathy
- Extensive disseminated and painful eruptions on the head and upper body; erythematous skin with multiple, round, umbilicated vesicles

Herpetic whitlow

- ⇒ Pathogen → HSV-1 in 60% of cases; HSV-2 in 40% of cases (in the adult population)
- ⇒ **Aetiology** → Direct contact with infected secretions
- ⇒ Risk factors
 - Children (via sucking of thumb/fingers (may have a history of labial herpes)
 - Health care workers exposed to oral secretions (e.g., dentists)
- ⇒ Incubation period: 2–20 days
- ⇒ Infection of the dermal and subcutaneous tissue
- ➡ Grouped, non-purulent vesicles on an erythematous base, may rupture or ulcerate, involved one or more fingers (especially the thumb and index fingers); mostly found on terminal phalanx.
- ⇒ Axillary and epitrochlear lymphadenopathy
- ⇒ Management → oral acyclovir

Investigations

- Nucleic acid amplification test (NAAT) are recommended as the preferred diagnostic method for genital herpes. now regarded as the test of choice.
 - ⇒ PCR (a type of NAAT) : detects HSV RNA; identification of virus genotype

Western blot

- the gold standard for the detection of antibodies to HSV, but it is not commercially available.
- ⇒ expensive, time consuming and requires skilled interpretation.
- ⇒ high sensitivity
- ⇒ have ability to discriminate between HSV-1 and HSV-2 antibodies.

Viral culture

- ⇒ gold standard for definitive diagnosis; 100% specificity for HSV-1 or HSV-2
- ⇒ The culture should be taken from a fresh vesicle, either from skin or genitals.
- Light microscopy findings on a Tzanck smear
 - ⇒ Detects multinucleated giant cells (nonspecific)
 - ⇒ Eosinophilic intranuclear Cowdry A inclusion bodies
 - ⇒ Unable to differentiate between HSV-1 and HSV-2, also commonly positive in VZV
 - ⇒ rarely used now for diagnosis.
 - ⇒ can be performed when an urgent result is needed and no alternative test is immediately available

Management

- Antiviral treatment reduces the severity of episodes but is not curative.
- gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest

- genital herpes: oral aciclovir.
 - ⇒ Topical anaesthetic agents, e.g. 5% lidocaine (lignocaine) ointment
 - ⇒ Recommended regimens : Aciclovir 400 mg three times daily OR Valaciclovir 500 mg twice daily (for 5 days)
 - ⇒ Some patients with frequent exacerbations may benefit from longer term aciclovir
 - more than six herpes episodes over the past 12 months → trial of suppressive therapy (aciclovir 400 mg BD for 12 months).
 - **⇒** Genital herpes in pregnant lady:
 - Aciclovir is considered safe and well tolerated.
 - If genital herpes is not recurrent and healed after a course of aciclovir:
 - There is no need to continue suppressive therapy throughout the pregnancy.
 - Restart acyclovir 400 mg TDS suppressive dose from week 36 to prevent active lesions being present at the time of delivery, where caesarean would definitely be needed.
 - If there is a history of recurrent genital herpes → she should continue taking acyclovir 400 mg TDS until the end of the pregnancy
 - If there are active lesions or prodromal symptoms at the time of delivery
 → A caesarean section should be considered

Early treatment of herpes infections is essential to prevent complications because antiviral drugs only inhibit the virus during its replication phase



Yellow fever

• Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

Aetiology

- Pathogen: yellow fever virus (genus Flavivirus)
- linear RNA virus
- spread by Aedes mosquitos (primarily Aedes aegypti)
- incubation period = 2 14 days

Epidemiology

endemic in large parts of South America and Africa but not in Asia.

Features

- Most patients remain asymptomatic
- In symptomatic patients: classic progression in three stages
 - 1. Period of infection (3–4 days)

- Sudden onset of fever (up to 41°C)
- Headaches, chills
- Nausea, vomiting
- Bradycardia may develop
- 2. Period of remission (up to 2 days)
 - Easing of symptoms and decline in fever
- 3. Period of intoxication (only in \sim 15% of symptomatic patients)
 - Hemorrhage
 - Multiorgan dysfunction (e.g., acute kidney and liver failure)
 - Nausea, (bloody) vomiting, abdominal pain, severe jaundice
 - ❖ Zone 2 of the liver is most affected in Yellow fever.

Yellow fever is suggested by:

- 1. Travel to endemic area (West Africa and Central America)
- 2. Fever, with initial resolution
- 3. Progression to jaundice and renal failure

Investigations

- Leukopenia
- Thrombocytopenia, ↑ PTT
- Signs of organ failure (acute liver failure, acute renal failure)
- Virus detection
 - ⇒ PCR: the best test to rule out yellow fever infection is PCR
 - ⇒ ELISA
- Liver biopsy
 - ⇒ Used for definitive diagnosis (e.g., postmortem)
 - ⇒ Must not be done while the patient has an active yellow fever infection
 - ⇒ May show Councilman bodies
 - Councilman bodies (inclusion bodies) may be seen in the hepatocytes
 - For exam purposes Councilman bodies (eosinophilic inclusion in the liver on post mortem) are diagnostic of yellow fever, although they can occasionally be seen in other Viral Haemorrhagic Fevers such as Crimean Congo Haemorrhagic Fever, (but this is nosocomially spread)

Treatment

- Symptomatic treatment
- No specific antiviral treatment is available

Prevention

- Yellow fever vaccine
 - ⇒ the vaccination is the only intervention which could prevent death.
 - a live, attenuated vaccine that consists of the 17D strain of the virus, grown in hens' eggs.
 - ⇒ Administration
 - A single dose is provides life-long protection
 - administer at least 10 days before traveling to endemic area.
 - ⇒ Its use is contraindicated in:
 - Under six months
 - With previous confirmed anaphylactic reaction to the vaccine
 - previous confirmed anaphylactic reaction to egg
 - thymus disorder
 - immunocompromised due to a congenital condition, disease process or treatment.

Human immunodeficiency virus (HIV)

Aetiology

- · Consists of the two species :
 - ⇒ HIV-1: most common species worldwide
 - ⇒ HIV-2: restricted almost completely to West Africa

Pathophysiology

- HIV attaches to the CD4 receptor on host cells with its qp120 glycoprotein (binding)
- For fusion, CD4 receptor and a coreceptor (CCR5 in macrophages, and CCR5 or CXCR4 in T-cells) must be present.
 - ⇒ Viral entry into macrophages via CCR5 mainly occurs during the early stages of infection, while entry via CXCR4 occurs in later stages.
 - ⇒ Individuals without CCR5 receptors appear to be resistant to HIV, those patients either have a homozygous CCR5 mutation (substantial resistance) or a heterozygous CCR5 mutation (slower course).
- gp120 is the HIV glycoprotein that can cross the placenta and infect the fetus.
- The lymph nodes are the organs in which HIV replicates during the latent phase.

Associations

 Epstein-Barr virus reactivation, leading to B-cell lymphoma, typically occurs in AIDS patients with a CD4+ cell count less than 100/mm³.

Routes of transmission

- Sexual: responsible for ~ 80% of infections worldwide
- Parenteral transmission
- Needle sharing: → 0.67%
- Vertical transmission: from mother to child during childbirth (~ 5–15%)

Features

- In early HIV infection, patients are often asymptomatic.
- Acute HIV infection (acute retroviral syndrome) (ARS)
 - ⇒ Typically occurs 2-12 weeks after infection
 - ⇒ Fever, Fatique, Myalgia and arthralgia
 - ⇒ Generalized nontender lymphadenopathy
 - ⇒ Generalized rash
 - ⇒ Gastrointestinal symptoms (nausea, diarrhea, weight loss)
 - ⇒ Oropharyngeal symptoms (sore throat, ulcerations, painful swallowing)
- Clinical latency and AIDS
 - ⇒ Clinical latency: Infected individuals may still be asymptomatic.
 - Non-AIDS-defining conditions (common when CD4+ count is below 500 cells/mm3)
 - Generalized lymphadenopathy
 - Chronic diarrhea (> 1 month)
 - Localized opportunistic infections
 - Oral candidiasis: creamy, white patches on the mucous membranes of the mouth that can be scraped off
 - Oral hairy leukoplakia: lesions that cannot be scraped off located mainly on the lateral borders of the tongue; triggered by Epstein-Barr virus
 - HPV-related: squamous cell carcinoma of the anus (common in men who have sex with men) or cervix
 - molluscum contagiosum, warts; shingles
 - **⇒** AIDS-defining conditions
 - Kaposi sarcoma (typically occurs at CD4 count < 500)

- Mycobacterial infections (e.g, TB)
- Progressive multifocal leukoencephalopathy (typically occurs at CD4 count < 200)
- Disseminated or extrapulmonary coccidioidomycosis (occurs at CD4 count < 250)
- Pneumocystis pneumonia (occurs at CD4 count < 200)
- Disseminated or extrapulmonary histoplasmosis (occurs at CD4 count < 150)
- Conditions occurs at CD4 count < 100
 - Cerebral toxoplasmosis
 - Extrapulmonary cryptococcosis (especially cryptococcal meningitis)
 - Esophageal candidiasis or pulmonary candidiasis
 - Herpes simplex Esophagitis
 - Primary CNS lymphoma
- Conditions occurs at CD4 count < 50
 - Disseminated and/or extrapulmonary Mycobacterium avium complex
 - Cytomegalovirus infection

Unlike oral candidiasis, esophageal candidiasis is an AIDS-defining condition.

Man returns from trip abroad with maculopapular rash and flu-like illness - think HIV seroconversion

WHO (World Health Organization) classification

- **Primary HIV infection:** acute retroviral syndrome or asymptomatic
- Clinical stage 1: persistent generalized lymphadenopathy (PGL) or asymptomatic
- Clinical stage 2: e.g., unexplained moderate weight loss (< 10%), recurrent fungal/viral/bacterial infections
- Clinical stage 3: e.g., unexplained severe weight loss (> 10%), unexplained chronic diarrhea (> 1 month), unexplained persistent fever (≥ 37.6°C intermittent or constant > 1 month), persistent/severe fungal/viral/bacterial infections, unexplained anemia (< 8 g/dL) and/or neutropenia (< 500 cells/mm3) and/or chronic thrombocytopenia (< 50,000/µL) for more than 1 month
- Clinical stage 4: AIDS-defining conditions (e.g., Kaposi sarcoma, Pneumocystis pneumonia)

Diagnosis

- HIV-1/2 antigen/antibody combination immunoassay (Ag/Ab immunoassay) (ELISA)
 - ⇒ Target of detection: IgM and IgG antibody and p24 antigen
 - ⇒ Approximate time to positivity: 15 to 20 days after event
 - ⇒ If a very early infection is suspected (less than 2 weeks), advice for:
 - Serial testing at 1 month and again at 3 months from the date of the possible exposure OR
 - HIV RNA viral load test
 - ⇒ p24 is the **capsid** protein of HIV, coded for by the *gag* gene.
 - ⇒ If negative → No further testing is required (exclude HIV)
 - ⇒ If positive → confirm by HIV-1/2 differentiation immunoassay (differentiates HIV-1 antibodies from HIV-2 antibodies)

· HIV viral load test

- ⇒ Made by PCR of peripheral blood for HIV RNA
- ⇒ Target of detection: RNA
- ⇒ Approximate time to positivity: 5 15 days
- ⇒ In acute HIV the viral load is very high.

HIV-1/2 differentiation immunoassay

- ⇒ Confirmatory test, indicated following a positive HIV-1/2 Ag/Ab immunoassay
- ⇒ The differentiation assay is now the standard confirmatory test
- ⇒ Determines whether it is HIV-1 or HIV-2 infection
- ⇒ If both Ag/Ab immunoassay and differentiation immunoassay are positive → confirm diagnosis of HIV and determine as positive for HIV-1 antibodies, HIV-2 antibodies, or HIV antibodies, undifferentiated.
- ⇒ If Ag/Ab immunoassay differentiation was positive but differentiation immunoassay is negative (non-reactive) → test for HIV-1 nucleic acid test (NAT).

HIV-1 nucleic acid test (NAT)

- ⇒ A reactive HIV-1 NAT result and nonreactive HIV-1/HIV-2 antibody differentiation immunoassay result indicates laboratory evidence for **acute HIV-1 infection**.
- ⇒ A negative HÍV-1 NAT and nonreactive or indeterminate HIV-1/HIV-2 antibody differentiation immunoassay indicates a false-positive result on the initial immunoassay
- Flow cytometry is the lab technique used to measure CD4 cell count
 - ⇒ Used to determine the level of immune suppression once an infection is confirmed.
 - ⇒ The most useful investigation in estimating the risk of developing an opportunistic infection
 - ⇒ A count lower than 200/mm³ generally indicates progression to AIDS.
- The Centers for Disease Control (CDC) no longer recommends Western blot confirmatory testing for HIV.

Treatment

- Since late 2015, the World Health Organization (WHO) has recommended starting ART in every HIV-positive individual, regardless of CD4 count.
- In hepatitis B co-infection
 - Antiretrovirals that also have anti-HBV activity should be included in the regimen used to treat HIV. These include:
 - Emtricitabine
 - Lamivudine
 - Tenofovir
 - ⇒ Discontinuation of drugs that have anti-HBV activity can lead to reactivation of HBV and cause serious hepatocellular damage.
- In patients with renal impairment → avoid **tenofovir** and consider avoiding atazanavir.

Initiation of ART should be delayed in the setting of TB meningitis and cryptococcal meningitis because of the high risk of immune reconstitution syndrome

Stopping NRTIs in patients with hepatitis B co-infection can lead to an acute worsening of their hepatitis!

HIV and pregnancy

Efavirenz is the only antiretroviral medication that is contraindicated in pregnancy (teratogenic)

Epidemiology

• In London the incidence may be as high as 0.4% of pregnant women.

Factors which reduce vertical transmission (from 25-30% to 2%)

- maternal antiretroviral therapy
- mode of delivery (caesarean section)
- neonatal antiretroviral therapy
- infant feeding (bottle feeding)

Screening

• NICE guidelines recommend offering HIV screening to all pregnant women

Treatment

• The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.

Antiretroviral therapy

- ⇒ all pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously
- ⇒ if women are not currently taking antiretroviral therapy the RCOG recommend that it
 is commenced between 28 and 32 weeks of gestation and should be continued
 intrapartum. BHIVA recommend that antiretroviral therapy may be started at an
 earlier gestation depending upon the individual situation
- ⇒ No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses.
- ⇒ It is recommended that women conceiving on an effective anti-retroviral (ART)
 regimen should continue this even if it contains efavirenz or does not contain
 zidovudine. Exceptions are:
 - (1) Protease inhibitor (PI) monotherapy should be intensified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta.
 - (2) The combination of stavudine and didanosine should not be prescribed in pregnancy.

Mode of delivery

- ⇒ vaginal delivery is recommended if viral load is less than 50 copies/ml at 36 weeks, otherwise caesarian section is recommended
- ⇒ zidovudine infusion should be started four hours before beginning the caesarean section

Neonatal antiretroviral therapy

- zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used. Therapy should be continued for 4-6 weeks.</p>
- Infant feeding: in the UK all women should be advised not to breast feed

HIV: anti-retrovirals

HIV drugs, rule of thumb:

- · NRTIs end in 'ine'
- · Pis: end in 'vir'
- · NNRTIs: nevirapine, efavirenz

Anti-retroviral therapy for HIV is now started at the time of diagnosis, rather than waiting for the CD4 count to drop to a particular level

HIV: anti-retrovirals - P450 interaction

- nevirapine (a NNRTI): induces P450
- protease inhibitors: inhibits P450

Overview

- · Start HAART as soon as possible after diagnosis regardless CD4 count.
- Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging
 - ⇒ Atripla® (efavirenz, tenofovir, emtricitabine) is an acceptable choice.

Nucleoside analogue reverse transcriptase inhibitors (NRTI) (ine at the end)

Emtricitabine causes hyperpigmentation of skin including palmar creases in 8% of black patients.

- examples: zidovudine (AZT), lamivudine, stavudine, didanosine, zalcitabine
- general NRTI side-effects:
 - ⇒ Peripheral neuropathy
 - ⇒ Mitochondrial toxicity → dilated cardiomyopathy
 - NRTI → reduce vascular responsiveness to acetylcholine → endothelial dysfunction.
 - Mitochondrial dysfunction induced by HAART → decreased myocardial contractility. This is because cardiac myocytes can utilise energy less well, leading to decreased ejection fraction and dilative cardiomyopathy.
 - myocardial biopsy usually reveals mitochondria full of myelin, a sign of mitochondrial dysfunction.
 - Withdrawal of zidovudine and substitution with an agent associated with less mitochondrial toxicity, coupled with appropriate treatment for heart failure with diuretics and ACE inhibition, usually resolves the problem, although HIV itself is decreasingly recognised as a cause of cardiomyopathy.
- · zidovudine: anaemia, myopathy, black nails
 - ⇒ most frequently causes anaemia, usually by bone marrow suppression and patients can become transfusion-dependent in severe cases.

- Macrocytosis is a typical finding in patients on zidovudine and can be used as a parameter to monitor adherence to therapy.
- ⇒ Other side-effects of zidovudine include:
 - Myalgia, Myopathy, Myositis
 - **❖** Elevated CK → a picture of rhabdomyolysis
 - Pancytopenia,
 - Lactic acidosis.
 - Blue or black discolouration of the nails is a rare side-effect. May be misdiagnosed as cyanosis and melanoma.
- Didanosine: pancreatitis (Didanosine and stavudine cause mitochondrial toxicity, hence peripheral neuropathy, pancreatitis and hyperlactataemia.)
- NRTIs in particular <u>stavudine</u>, didanosine and zidovudine classically cause mitochondrial toxicity as an unwanted side effect. This can result in nausea, pancreatitis, lactic acidosis and lipoatrophy
- Truvada → combination of two (Nucleoside analog reverse-transcriptase inhibitors (NRTIs) : tenofovir disoproxil and emtricitabine
 - ⇒ tenofovir may cause:
 - 1. life-threatening liver damage
 - 2. lactic acidosis
 - sudden worsen of hepatitis B after stopping tenofovir → lab tests regularly for several months after stop.
- Abacavir: (the only NARTI which is not ended by (ine))
 - ⇒ is a nucleoside reverse transcriptase inhibitor (NRTI).
 - ⇒ It is recommended by the British HIV Association (BHIVA) in association with lamivudine as an alternative to Truvada as part of a HAART regime.
 - Abacavir causes a hypersensitivity reaction in patients who are <u>HLA-B5701</u> positive.
 - However, this would occur within 1–2 months of starting treatment
 - in the UK all patients would be tested prior to initiation.
 - It is typified by nausea, vomiting, malaise and fever, with or without a rash.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (vir in the middle)

- Examples: nevirapine, delavirdine, efavirenz and etravirine.
- Side-effects:
 - ⇒ P450 enzyme interaction (nevirapine induces),
 - ⇒ Skin rashes
 - Rashes are common on starting treatment with <u>nevirapine</u>, occurring in ~15% of patients.
 - Nevirapine can cause acute hepatitis and skin rash as a part of hypersensitive reaction
 - this is the rationale for starting low-dose therapy with nevirapine in the first 2 weeks
 - Serious side effects are more common in patients with relatively well preserved immune function.
 - ⇒ Acute hepatitis
 - **⇒** Efavirenz side effects
 - more common → neuropsychiatry side effects.
 - less common → Gynaecomastia

Efavirenz is the most common HAART drug associated with gynecomastia.

Protease inhibitors (PI) (vir at the end)

- Examples: indinavir, nelfinavir, ritonavir, saquinavir
- · Side-effects:
 - ⇒ diabetes,
 - ⇒ hyperlipidaemia, Hypertriglyceridaemia
 - ⇒ Buffalo hump, central obesity,
 - ⇒ P450 enzyme inhibition
 - ⇒ Lipodystrophy
 - ⇒ Indinavir: → renal stones, asymptomatic hyperbilirubinaemia
 - ⇒ Ritonavir:
 - Potent inhibitor of the P450 system (3A4 inhibitor)
 - Produces very significant elevations in plasma fluticasone (even an inhaled preparation).
 - so, it increases the levels of rifampin.
 - These levels are sufficient to suppress endogenous cortisol levels and produce Cushing's syndrome.

Co-trimoxazole prophylaxis for *Pneumocystis* (PCP) is not necessary unless the CD4 count is below 200

Patient who have high viral load despite treatment:

- Causes of treatment failure:
 - ⇒ poor adherence
 - ⇒ drug interactions or absorption issues
 - ⇒ primary resistance or superinfection with a new resistant strain.
- All patients should have had a resistance test at baseline
 - The most appropriate course of action is to <u>arrange an urgent resistance test</u> and manage the antiretrovirals accordingly with this result.

Patient who have TB associated with HIV:

• Efavirenz is used in combination with an NRTIs because it has little effect on the plasma levels of rifampin which is being used to treat the pulmonary tuberculosis.

Preventing Opportunistic Infections in Patients With HIV

- Initiation of Prophylaxis and Treatment
 - ⇒ Patients not taking ART who present with disseminated Mycobacterium avium complex (MAC) infection should be treated for the infection without ART for 2 weeks, and then started as soon as possible on ART while monitored closely for symptoms of the immune reconstitution inflammatory syndrome (IRIS).
 - ⇒ Severe IRIS has also been reported after early ART in the management of <u>cryptococcal and tuberculous meningitis</u>, and it has been suggested that such patients delay ART until 4-6 weeks after control of the opportunistic infection.
 - ⇒ Patients with CD4 counts of less than 50 cells/µL at presentation should be considered for cryptococcal antigen testing,
 - ⇒ among those diagnosed with cryptococcal meningitis, initial ART should be delayed at least 2 weeks into cryptococcal therapy and as long as 10 weeks.
 - which must be treated initially with amphotericin and flucytosine.
- CD4 counts are useful landmarks for initiation of antimicrobial prophylaxis:
 - Less than 250 cells/μL Coccidioidomycosis prophylaxis if seropositive in high-risk area

- Patients with a new positive immunoglobulin M (IgM) or IgG serologic test result who live in endemic areas and have a CD4 count of less than 250 cells/µL should receive fluconazole 400 mg PO daily
- ⇒ Less than 200 cells/µL PCP prophylaxis
 - The preferred regimen is trimethoprim-sulfamethoxazole 1 double-strength tablet orally daily or 1 double-strength tablet orally 3 times weekly.
- ⇒ Less than 150 cells/µL Histoplasmosis prophylaxis if high-risk exposure
 - Patients with a CD4 count of less than 150 cells/µL at high risk for exposure or who live in a hyperendemic area should receive itraconazole 200 mg PO daily
- ⇒ Less than 100 cells/µL Toxoplasmosis prophylaxis (if seropositive)
 - Trimethoprim-sulfamethoxazole, one double-strength tablet orally once daily is preferred
- ⇒ Less than 100 cells/µL Penicilliosis prophylaxis if living in high-risk area
- ⇒ Less than 50 cells/µL MAC infection prophylaxis
 - Patients with CD4 count of fewer than 50 cells/µL should be given azithromycin 1200 mg orally weekly after ruling out disseminated MAC infection on clinical assessment
 - Alternatives include clarithromycin 500 mg orally twice daily or rifabutin 300 mg orally daily
- Clinical Landmarks for Terminating Primary Prophylaxis
 - ⇒ *Mycobacterium avium-intracellulare* (MAI) infection prophylaxis:
 - should be continued with antiretroviral therapy (ART) until the CD4 count exceeds 100 cells/µL for 3 months.
 - ⇒ *P carinii* pneumonia (**PCP**) and **toxoplasmosis** prophylaxis:
 - should be continued until the CD4 count exceeds 200 cells/µL for 3 months.
 - ⇒ Histoplasmosis prophylaxis:
 - can be discontinued when the CD4 count has exceeded 150 cells/µL for 6 months.
 - ⇒ coccidioidomycosis prophylaxis:
 - can be discontinued when CD4 counts exceed 250 cells/µL for 6 months,
 - ⇒ penicilliosis prophylaxis:
 - can be discontinued when CD4 counts exceed 100 cells/µL for 6 months.

HIV lipodystrophy (Antiretroviral-related lipodystrophy)

- Lipodystrophy (loss of adipose tissue), lipoatrophy and alterations in serum lipid values have been observed in patients with human immunodeficiency virus (HIV) disease taking highly active antiretroviral therapy (HAART).
- Consequences
 - ⇒ ↑serum lipid levels → premature coronary artery disease.
 - ⇒ Hypertriglyceridaemia → central fat deposition and insulin resistance
 (Antiretroviral insulin-resistance syndrome)
 - there is some evidence that the insulin sensitisers (glitazones) may be effective in some patients

Causes

- Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease but appear much commoner in patients taking protease inhibitors.
- ⇒ Isolated <u>hypertriglyceridaemia</u> can occur in HIV disease in the absence of <u>protease inhibitors</u> but extremely high serum triglycerides have been documented in some patients treated with these drugs.

Treatment

- ⇒ Mild to moderate hyperlipidaemia → 1st line dietary modification and exercise
- ⇒ Predominant **hypercholesterolaemia** or with a mixed picture → statin
 - Caution must be exercised since some protease inhibitors interact with some statins due to metabolism by CYP3A4 pathway.
 - Simvastatin is contraindicated in patients on protease inhibitors and plasma levels of atorvastatin are also greatly elevated in these patients.
 - For this reason, pravastatin is usually the drug of choice.
 - Pravastatin is preferred because its metabolism is not as dependent on the CP450s as other agents in this group.
- **⇒** Hypertriglyceridaemia → fenofibrate
- ⇒ Switching therapy might be an option, to non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- ⇒ In women with lipoatrophy syndromes, oral estrogens should be avoided as they can exacerbate the hypertriglyceridemia and result in acute pancreatitis.

Immune reconstitution syndrome

- Due to activation of the immune system following HIV therapy against persisting antigen.
- Typically occurs a few weeks after commencing anti-retroviral therapy in a patient with underlying tuberculosis.

HIV: biliary and pancreatic disease

- The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia
- Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV

HIV: diarrhoea

Supportive therapy is the mainstay of treatment in Cryptosporidium diarrhoea

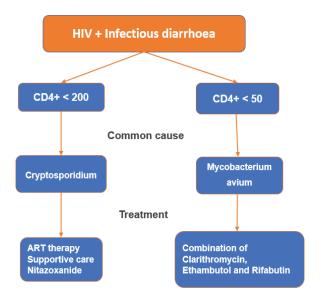
Diarrhoea is common in patients with HIV.

Causes

- Infection, may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections (usually there are fever and wasting)
- Malignancy (infiltrative diseases, such as lymphoma or Kaposi's sarcoma.),
- Medications (e.g. antiretroviral therapy, particularly when diarrhea is the sole presenting symptom and there is a temporal association.)
 - Ritonavir-containing protease inhibitors (PIs) are the drugs most commonly associated with diarrhoea.

Infectious causes

- Cryptosporidium (the most common cause of diarrhoea in HIV patients who their CD4+ > 50)
 - ⇒ It is an intracellular protozoa and has an incubation period of 7 days.
 - ⇒ Presents as watery diarrhoea, often with severe abdominal pain, commonly lasting >7 days.
 - ⇒ Diagnosis: usually by detection of *Cryptosporidium* oocysts, antigens, or DNA in stools.
 - ⇒ Treatment:
 - Supportive therapy is the mainstay of treatment
 - If patient is not on antiretroviral therapy (ART): initiation of ART is the primary intervention
 - Nitazoxanide may be used for treatment (Antiprotozoal)
- · Mycobacterium avium intracellulare
 - ⇒ is an atypical mycobacteria seen with the CD4 count is below 50.
 - ⇒ Presentation: fever, sweats, abdominal pain and diarrhoea. There may be hepatomegaly and deranged LFTs.
 - ⇒ Diagnosis is made by blood cultures and bone marrow examination.
 - ⇒ Management is with combination of clarithromycin, ethambutol and rifabutin



HIV nephropathy

Overview

- Accounts for up to 10% of end-stage renal failure cases in the United States.
- Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself.
- Protease inhibitors such as indinavir can precipitate intra-tubular crystal obstruction

Features

- Raised creatinine
- Nephrotic range proteinuria
- Normal sized kidneys on ultrasound scan,
- Focal segmental glomerulosclerosis on renal biopsy.
- Raised immunoglobulins
- Raised cholesterol
- Normotension

Cryptococcal disease in AIDS (Cryptococcosis)

Epidemiology

- The most common fungal infection of the CNS
- · The most common fungal disease in HIV

Features

- May present as: space-occupying lesion, meningitis, or meningoencephalitis.
- Symptoms are typically of gradual onset over one to two weeks.

Risk factors

usually develops only when CD4+ lymphocyte counts fall below 100 cells/mL.

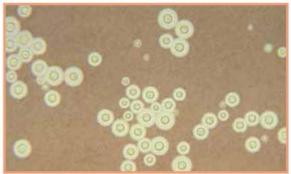
Diagnosis

• MRI, with and without contrast, is the preferred diagnostic imaging modality.

- The India ink test is used to diagnose cryptococcal meningitis,
- the raised opening pressure, turbid appearance to the CSF, raised protein and mixed lymphocytic/neutrophil picture are relatively typical of the diagnosis.

Treatment

- Treatment is with amphotericin B and flucytosine (5FC);
- patients then require lifetime suppression with <u>fluconazole</u>.



Microscopy of Cryptococcus neoformans.

Cryptococcus neoformans skin lesions

- Most often seen in T cell deficiency states and HIV-infected patients with CD4 counts of <100/mm³.
- Gomori's methanamine silver stain shows budding yeasts.
- Serum cryptococcal antigen can also be used in diagnosis.
- Treatment is with an eight-week course of fluconazole 400 mg /day followed by 200 mg/day.

HIV: immunisation

The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

Vaccines that can be used in all HIV-infected adults	Vaccines that can be used if CD4 > 200	Contraindicated in HIV- infected adults
 Hepatitis A Hepatitis B Haemophilus influenzae B (Hib) Influenza-parenteral Japanese encephalitis Meningococcus-MenC Meningococcus-ACWY I Pneumococcus-PPV23 Poliomyelitis-parenteral (IPV) Rabies Tetanus-Diphtheria (Td) 	Measles, Mumps, Rubella (MMR) Varicella Yellow Fever	 Cholera CVD103-HgR Influenza-intranasal Poliomyelitis-oral (OPV) Tuberculosis (BCG)

Routine vaccines

- People with HIV are at risk of Hep B, invasive pneumococcal disease and severe morbidity from influenza. These are all inactivated vaccines and can be given at any CD4 count.
- Should be vaccinated against Hepatitis B, pneumococcus, and yearly against
 - Hepatitis B is given as a course of three injections at double dose and booster as required.
 - pneumococcal vaccine PPV23 is a single dose but could be boosted 5-10 years later.
 - influenza vaccine should be administered yearly.

Other vaccines

- Men C vaccine → only recommended in people under 25.
- polio vaccine
 - ⇒ the oral polio vaccine is not recommended in HIV as it is a live vaccine.
 - ⇒ However, the parenteral polio vaccine is acceptable.
- MMR vaccine
 - ⇒ It is a live vaccine that is contraindicated in patients with a CD4 count of less than 200 cells/µL but could be safely administered in patient with CD4 count above 200 cells/µL.
- Haemophilus influenzae B vaccine
 - ⇒ is an inactivated vaccine that can be given to patients at any CD4 count.
 - ⇒ Although *Haemophilus influenzae* is an issue in people with HIV it is the pneumococcal vaccine that is recommended for all HIV patients.
 - ⇒ it is only recommended for those who have:
 - splenic dysfunction,
 - recurrent pulmonary infections
 - previous Haemophilus influenzae disease with risk of recurrence.
- shingles vaccine
 - ⇒ thought to be safe and immunogenic even in those who have recently had shingles.
 - ⇒ However, it must be used with caution in any immunocompromised state
 - should not be used in patients with a CD4 count of less than 200 cells/μL.

HIV: Kaposi's sarcoma

Kaposi's sarcoma - caused by HHV-8 (human herpes virus 8)

Overview

- Kaposi sarcoma is a neoplasm of endothelial cells (vascular tumor) that is caused by human herpes virus 8 (HHV-8)
- most commonly seen in patients with HIV and transplant patients.
 - ⇒ can be seen in HIV patients with a CD4+ cell count of less than 500/mm³.
- Human herpes virus 8, which causes Kaposi sarcoma in HIV patients, is transmitted by sexual contact.
- · Aside from affecting the skin, Kaposi sarcoma can also affect the gastrointestinal tract and lungs.

Feature

- presents as purple papules or plaques on the skin or mucosa (e.g. gastrointestinal and respiratory tract)
- · lesions occur most commonly on the face

- skin lesions may later ulcerate
- respiratory involvement may cause massive haemoptysis and pleural effusion, Chest x ray may show pulmonary nodules.
- · Histopathology classically show
 - ⇒ lymphocytic inflammation.
 - ⇒ proliferation of endothelial cells (spindle cells)

Treatment

- Radiotherapy + resection
 - ⇒ Radiotherapy may be used to treat painful or highly visible lesions.
- AIDS-related Kaposi's sarcoma becomes smaller as immune function improves such as with treatment with highly active antiretroviral therapy (HAART).
- In some circumstances chemotherapy may be added to HAART.
- Human herpes virus 8 is also associated with:
 - ⇒ primary effusion lymphoma (a rare lymphoma of serous cavities)
 - ⇒ Castleman's disease.



Kaposi's sarcoma in a patient with HIV

HIV: Dermatologic conditions (Eosinophilic folliculitis) (EF)

Overview

 Dermatologic conditions are very common in HIV/AIDS infection; knowing the common infections and their treatment is important.

Types

- There are three main variants of Eosinophilic folliculitis (EF):
- Classic EF immunosuppression-related EF (mostly HIV-associated) and Infancy-associated EF.
- The most common type of EF is the immunosuppression-related (HIV-associated) form.
- The clinical presentations of EF vary slightly, but histologically the forms are identical.
- Classic EF
 - ⇒ also known as Ofuji disease (eosinophilic pustular folliculitis)
 - ⇒ more common in individuals of Japanese descent, although anyone can be affected.

• Immunosuppression-EF

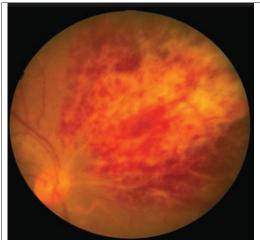
- ⇒ Differs from the classical form in that the eruption is exquisitely pruritic. It also tends to present with erythematous, almost oedematous, papules with few pustules (whereas the classic form tends to have clusters of pustules).
- ⇒ Because the eruption is so pruritic the lesions are often excoriated on presentation, making identification of a primary lesion difficult.
- ⇒ The lesions are found primarily on the face and upper trunk (from the waist up).
- ⇒ **Histologic examination** of a papule shows an acute and chronic infiltrate of eosinophils and lymphocytes focused at the level of the follicular isthmus that can rarely progress to complete follicular destruction.
- ⇒ Men more commonly affected than women.
- may worsen 3 6 months after initiation of antiretroviral therapy as part of the immune restoration syndrome and even after the CD4+ cell count rises above 200/μL.

HIV: abnormal vaginal bleeding

- Abnormal bleeding can be a sign of cervical dyskaryosis.
- Advanced HIV with HPV co-infection is a very strong risk factor for developing cervical dyskaryosis and currently the British HIV association recommend that patients with HIV should have yearly smears.
- The US guidelines recommend that HIV positive females under the age of 26 and MSM should be immunised as the HPV vaccine is safe and immunogenic at all CD4 counts.
- The risk of HPV infection already present is too great in patients older than 26 for cost effectiveness.
- In Britain the national programme now immunises all females aged 12-13 years.
- If cervical dyskaryosis is detected it is treated in the same way as in HIV negative patients.
- HIV patients should have a yearly smear as per the current BHIVA guidelines. This
 may change as more information is gathered about cervical disease in patients who are
 stable on ARVs.
- Cervical dyskaryosis is invisible to the naked eye and so a normal speculum examination does not rule out cervical disease.

CMV retinitis in a patient with HIV

• AIDS retinitis is typically caused by cytomegalovirus.



The slide shows the typical 'cottage cheese and tomato ketchup' or 'pizza' appearance of CMV retinitis in a patient with HIV disease.

Vaginal discharge

Vaginal discharge is a common presenting symptom and is not always pathological

Common causes	Less common causes
 physiological Candida Trichomonas vaginalis bacterial vaginosis 	 Gonorrhoea Chlamydia can cause a vaginal discharge although this is rarely the presenting symptoms ectropion
	foreign body
	 cervical cancer

 Black women report higher incidence of candidiasis infections compared with white women.

Key features of the common causes are listed below

Condition	Key features	
Candida	'Cottage cheese' dischargeVulvitisItch	
Trichomonas vaginalis	 Offensive, yellow/green, frothy discharge Vulvovaginitis Strawberry cervix 	
Bacterial vaginosis	Offensive, thin, white/grey, 'fishy' discharge	

Bacterial vaginosis (BV)

Bacterial vaginosis - overgrowth of predominately Gardnerella vaginalis

Pathogen

• Bacterial vaginosis (BV) describes an overgrowth of predominately anaerobic organisms such as *Gardnerella vaginalis*.

Epidemiology

 BV is the commonest cause of abnormal vaginal discharge in women of childbearing age. It is twice as common as vaginal candidiasis.

Risk factors

- intrauterine coil device.
- · vaginal douching
- number of sexual partners.
- Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually
 active women.

Features

- · vaginal discharge: 'fishy', offensive, Gray, thin, and homogeneous
- asymptomatic in 50%
- This leads to a consequent <u>fall in lactic acid producing aerobic lactobacilli</u> resulting in a raised vaginal pH.

Diagnosis

Epithelial cells with a stippled border (Clue cells) are the hallmark microscopic findings of bacterial vaginosis

- Amsel's criteria for diagnosis of BV 3 of the following 4 points should be present
 - 1. thin, white homogenous discharge
 - 2. clue cells on microscopy: stippled vaginal epithelial cells
 - 3. vaginal pH > 4.5
 - 4. positive whiff test (addition of potassium hydroxide results in fishy odour)

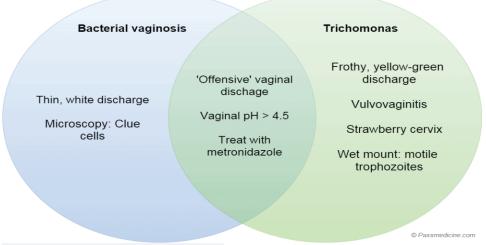
Management

Bacterial vaginosis treatment → oral metronidazole

- Infection resolves spontaneously in one-third of cases
- oral metronidazole (400 mg twice daily given for 5-7 days)
 - \Rightarrow initial cure rate \rightarrow 70-80%
 - ⇒ relapse rate > 50% within 3 months
- · the BNF suggests topical metronidazole or topical clindamycin as alternatives

Bacterial vaginosis in pregnancy

- complications
 - ⇒ results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage
- treatment
 - it was previously taught that oral metronidazole should be avoided in the first trimester and topical clindamycin used instead. Recent guidelines however recommend that oral metronidazole is used throughout pregnancy. The BNF still advises against the use of high dose metronidazole regimes



Comparison of bacterial vaginosis and Trichomonas vaginalis

MRCPUK-part-1-January 2020 exam: H/O offensive vaginal discharge. Diagnosed as bacterial vaginosis. What is the most appropriate initial management?

→ Oral metronidazole

Trichomonas vaginalis

Overview

- anaerobic flagellated protozoan, which thrive in more alkaline conditions.
- incubation period is 5 to 28 days.
- transmitted directly, for example, through sexual transmission.

Feature

- asymptomatic (in most men and 50% of women)
- yellow-green, frothy vaginal discharge
- vulvar pruritus
- dysuria, dyspareunia, and lower abdominal pain.
- Punctuate hemorrhages on the cervix, i.e. "strawberry cervix", or along the vaginal wall
 are less common signs, but are highly suggestive of infection with Trichomonas vaginalis.
- The PH of the discharge is greater than 4.5

Diagnosis

 The most rapid and practical method for detection is the use of a <u>wet mount</u> in clinic, which demonstrates <u>motile flagellated protozoans</u>.

Differential diagnosis

 Whilst bacterial vaginosis is also associated with a discharge with a fishy odour, classically there is no soreness or irritation associated with it.

Treatment

- A large dose of metronidazole (2 g as a single course), or a seven day course at lower dose is the treatment of choice.
 - ⇒ Single-dose therapy increases drug adherence.
 - ⇒ If standard treatment with either single-dose or multidose therapy fails, a regimen of 2 g of oral metronidazole or tinidazole for 5 days may be considered
 - ⇒ Patients should not consume alcohol during the course of treatment or during the 24 hours after the completion of the medication.
 - ⇒ Patients on tinidazole therapy should not consume alcohol during therapy or for 72 hours after completion of the medication.
 - Drinking alcohol while taking tinidazole causes disulfiram-like reaction, which includes (nausea, vomiting, headache, †BP, flushing, and shortness of breath).
 - ⇒ Tinidazole has a longer half-life (12-14 h) than metronidazole (6-7 h).
 - ⇒ metronidazole and tinidazole are equally effective

 \Rightarrow

Partner

⇒ **Partners** should be identified and also screened for infection as men rarely exhibit symptoms of a *T. vaginalis* infection.

- The epithelial damage caused by T. vaginalis increases susceptibility to HIV virus infection and transmission.
- ⇒ Both patient and partner should abstain from sex until pharmacological treatment has been completed and they have no symptoms.

. HIV-positive women with Trichomoniasis.

- ⇒ the CDC recommends considering the multidose treatment in HIV-positive women with Trichomoniasis.
 - (metronidazole 500 mg twice daily for 7 days) are more effective in treating T vaginalis in HIV-positive women than a single-dose treatment (metronidazole 2 g single dose).

In pregnant women

- ⇒ The CDC recommends that infected <u>symptomatic</u> pregnant women be considered for treatment, as metronidazole has not been definitively shown to be harmful during pregnancy and may prevent transmission to the newborn.
- ⇒ Infected <u>asymptomatic</u> pregnant women may wish to defer treatment to after 37 weeks' gestation.
- ⇒ Pregnant women should be treated with 2 g metronidazole in a single dose, according to the CDC.
- ⇒ The safety of tinidazole in pregnancy is not known.
- ⇒ Tinidazole is a pregnancy class C agent; animal studies have demonstrated adverse effects on fetal development. Its use is not recommended in pregnant women.

In breastfeeding women

⇒ In breastfeeding women, the CDC recommends stopping breastfeeding during the course of metronidazole treatment and for 12-24 hours after the last day. For treatment with tinidazole, the CDC recommends stopping breastfeeding for the course of treatment and for 3 days after the last dose.

Screening and Rescreening

- ⇒ Patients should be screened for other sexually transmitted infections.
- ⇒ the CDC recommends **rescreening at 3 months post therapy** for sexually active women, as they have a high rate of reinfection.

Genital ulcers (STI)

Genital ulcers:

- Painful: herpes much more common than chancroid
- Painless: syphilis more common than lymphogranuloma venereum + granuloma inguinale

Other causes of genital ulcers

- · Behcet's disease
- carcinoma
- granuloma inguinale: *Klebsiella granulomatis* (previously called *Calymmatobacterium granulomatis*)

Genital herpes

- Causes:
 - ⇒ most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1).
- Features:
 - Multiple painful penile vesicles and ulcers are characteristic.
 - ⇒ Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site.
- Diagnosis:
 - ⇒ Tzanck smear for lesions suspicious of HSV
- Treatment:
 - ⇒ Oral Acyclovir is the treatment of choice.
- Prognosis:
 - ➤ The lesions generally heal within 2 weeks.
 - Recurrence of painful genital lesions is a characteristic.

Chancroid

- Causes:
 - Haemophilus ducreyi.
- Features: (Remember the saying: "You do cry with ducreyi".)
 - ⇒ painful genital ulcers
 - The ulcers typically have a sharply defined, ragged, undermined border, which readily bleeds on contact.
 - ⇒ unilateral, painful inguinal lymph node enlargement.
- Diagnosis
 - ⇒ definitive diagnosis based on isolation of *H ducreyi* on special media
 - ⇒ polymerase chain reaction (PCR) = rapid detection of *H ducreyi*
 - ⇒ test for the other common STDs (syphilis, HSV, gonorrhea, chlamydia) and HIV.
- Treatment:
 - ⇒ Antibiotic treatment: single dose oral azithromycin or IM ceftriaxone
 - ⇒ Examine and treat sexual partner(s).

Lymphogranuloma venereum (LGV)

- Causes:
 - ⇒ (L1, L2 or L3 serovars of) Chlamydia trachomatis.
- Spread:
 - ⇒ The bacterium gains entry through breaches in the epithelial/mucous membranes, travelling through the lymphatics via macrophages to local nodes.
- Stages: three stages:
 - ⇒ **stage 1**: small painless pustule which later forms an ulcer at the site of inoculation 3-12 days later.
 - ⇒ **stage 2**: painful inguinal lymphadenopathy (Presents 1-6 months later).
 - Enlarged lymph nodes are known as buboes, they are often painful and can lead to thinning of the overlying skin causing abscesses.

- Groove sign is separation inguinal nodes by the inguinal ligament and is characteristic of the disease.
- ⇒ **stage 3**: proctocolitis (if rectally, then tenesmus, proctocolitis, strictures and fistulas can ensue. Cervicitis and urethritis are also common features.)

Diagnosis:

- ⇒ enzyme linked immunoassays or polymerase chain reaction of infected sample areas/pus.
 - Acute and convalescent sera can be used, but requires two samples 2 weeks apart.
- ⇒ Inclusion bodies in the cytoplasm of scraped tissue cells are identified by iodine staining.

Treatment:

- ⇒ Antibiotics either doxycycline or macrolides (azithromycin or erythromycin)
 - the most appropriate intervention → Doxycycline for 21 days
 - In patients where this is unsuitable, azithromycin is also thought to be effective.
- ⇒ surgical drainage/aspiration of the buboes or abscesses.

Complications:

- ⇒ genital elephantiasis,
- ⇒ hepatitis,
- ⇒ infertility,
- ⇒ pelvic inflammatory disease,
- ⇒ arthritis
- ⇒ fitz hugh curtis syndrome (Perihepatic adhesions).

Syphilis

Aetiology

- Syphilis is a sexually transmitted infection caused by the spirochaete *Treponema pallidum*.
- Risk and chance of infection after sexual contact:
 - Approximately one-third of sexual contacts of infectious syphilis will develop the disease.
- The incubation period is between 9-90 days

Stages

Primary syphilis

- ⇒ occurs 14 days to three months post exposure
- ⇒ chancre painless ulcer at the site of sexual contact
- ⇒ local non-tender lymphadenopathy
- ⇒ often not seen in women (the lesion may be on the cervix)



primary chancre associated with syphilis

Secondary syphilis

- ⇒ occurs one to six months following the primary infection.
- ⇒ caused by dissemination of the bacteria from the chancre, leading to systemic symptoms
- ⇒ systemic symptoms: fevers, malaise, lymphadenopathy
- ⇒ rash on trunk, palms and soles
- ⇒ buccal 'snail track' ulcers (30%)
- ⇒ condylomata lata
- ⇒ Iritis
- ⇒ Hepatitis
- ⇒ Early neurosyphilis:
 - Meningovascular syphilis
 - is a form of <u>early neurosyphilis</u> involving the small and medium sized intracranial vessels,
 - most commonly presents as a <u>stroke</u> involving the middle cerebral artery.



Classical palm lesions of secondary syphilis



More generalised rash of secondary syphilis

Tertiary syphilis

- ⇒ occurs in one-third of untreated patients around 15–30 years after initial infection.
- ⇒ It is divided into:
 - Gummatous syphilis (granulomatous lesions of the skin and bones) most common (15% of patients)
 - Cardiovascular syphilis, ascending aortic aneurysms
 - Late neurosyphilis.
 - general paralysis of the insane
 - ⇒ Gradual onset confusion
 - ⇒ Hallucinations
 - ⇒ Tremors
 - ⇒ Fits
 - ⇒ Cognitive impairment
 - ⇒ Hyperreflexia,
 - ⇒ Argyll-Robertson pupils
 - tabes dorsalis

Features of congenital syphilis

- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- saddle nose
- deafness

Investigation

- The diagnosis usually based on clinical features, serology and microscopic examination of infected tissue
- Both VDRL and TPHA are often positive in gummatous syphilis. However, in cardiovascular and neurosyphilis, TPHA is positive and VDRL is often negative.
- Serological tests can be divided into
 - ⇒ cardiolipin tests (not treponeme specific)

- syphilis infection leads to the production of non-specific antibodies that react to cardiolipin
- examples include VDRL (Venereal Disease Research Laboratory) & RPR (rapid plasma reagin)
- insensitive in late syphilis
- not specific
- becomes negative after treatment
- Causes of false positive cardiolipin tests
 - pregnancy
 - SLE, anti-phospholipid syndrome
 - ❖ TB

- leprosy
- malaria
- ♣ HIV

- ⇒ Treponemal specific antibody tests
 - example: TPHA (*Treponema pallidum* Haem Agglutination test)
 - more specific
 - remains positive after treatment

Management

- Benzylpenicillin
 - First line treatment
 - benzathine penicillin 2.4 million units given intramuscularly. This is administered either as a single dose or two doses given one week apart.
- Alternatives: doxycycline or erythromycin
 - may be given in patients with allergies to penicillins.
 - In case of severe penicillin allergy, a single dose of (2 g) azithromycin is the preferred option because it is effective and doesn't raise compliance issues.
- Jarisch-Herxheimer reaction
 - This is an acute febrile illness with headache, myalgia, chills and rigors starting within 12 hours of the first dose of treatment and resolving within 24 hours
 - It is thought to be due to the release of endotoxins following bacterial death
 - It is usually not important in early syphilis unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour.
 - ❖ It occurs in ~50% of patients with primary syphilis, 90% with secondary syphilis and 25% with early latent syphilis.
 - also occurs in Lyme disease and Q fever.
 - Patients should be counselled about the reaction prior to receiving therapy for syphilis.
 - the appropriate management → reassurance and paracetamol for symptom control

UK national guidelines on the management of syphilis 2015

- General advice
 - □ Infected patient should be advised to abstain from sex until any lesions (if any) have resolved or until two weeks after treatment completion
- First-line:
 - ⇒ Benzathine penicillin dose: 2.4 Mega units IM weekly for up to 3 weeks
 - ⇒ alternative : Procaine dose: 1.8–2.4 mega units IM daily for 14 days.
 - Only if benzathine penicillin is not available (due to the pain and multiple injections associated)
- second-line → oral azithromycin single dose.
- Treatment during pregnancy:
 - ⇒ first and second trimesters → give single dose benzathine penicillin;

- ⇒ third trimester → two doses of benzathine penicillin one week apart.
- Neurosyphilis:
 - ⇒ Procaine penicillin 1.8-2.4 units once daily (IM, for 14 days) with oral probenecid 500 mg four times a day.
 - ⇒ Tests for monitoring the effect of treatment → RPR/VDRL test
 - ⇒ Treponemal enzyme immunoassay (EIA)/chemiluminescent assay (CLIA), preferably detecting both IqM and IqG is the screening test of choice.

Genital warts

Genital warts - 90% are caused by HPV 6 & 11

Genital wart treatment

- · multiple, non-keratinised warts: topical podophyllum
- · solitary, keratinised warts: cryotherapy

Overview

- Genital warts (also known as condylomata accuminata) are a common cause of attendance at genitourinary clinics.
- They are caused by the many varieties of the human papilloma virus HPV, especially types
 6 & 11
- It is now well established that HPV (primarily types 16,18 & 33) predisposes to cervical cancer.
- HPV 16 is an oncogenic virus and causes squamous cell carcinomas in the oral cavity, cervix, anus and penis.

Features

- small (2 5 mm) fleshy protuberances which are slightly pigmented
- may bleed or itch

Management

- first-line → topical podophyllum or cryotherapy, depending on the location and type of lesion.
 - ⇒ Multiple, non-keratinised warts → best treated with topical agents
 - ⇒ solitary, keratinised warts → respond better to cryotherapy
- second line → topical imiquimod
- genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years

Chlamydia genitourinary infections

Pathogenesis: Chlamydia trachomatis, is an obligate intracellular pathogen.

Incubation period: 7-21 days

Epidemiology

• Chlamydia is the most prevalent sexually transmitted infection in the UK. Approximately 1 in 10 young women in the UK have Chlamydia.

Features

Asymptomatic in the majority of the patient

- Women: cervicitis (Muco-purulent discharge, postcoital bleeding), dysuria, dyspareunia →
 pelvic inflammatory disease, increased incidence of ectopic pregnancies, infertility and
 perihepatitis (Fitz-Hugh-Curtis syndrome)
- · Men: urethral discharge, dysuria

Diagnosis

Nuclear acid amplification tests (NAATs) is the investigation of choice

Management (2018 UK national guideline for the management of infection with Chlamydia trachomatis, published by: British Association for Sexual Health and HIV).

- 1st line: Doxycycline 100mg bd for 7 days is now recommended as first line treatment for uncomplicated urogenital, pharyngeal and rectal chlamydia infections.
- 2nd line: Azithromycin (1 g as a single dose), for those who cannot take doxycycline. It is also the **preferred option for pregnant individuals.**
- Patients are advised to avoid sexual contact for 7 from starting medication
- partner notification
 - all individuals who had sexual contact with the patient within the 60 days prior to infection or the most recent sex partner if the last contact was more than 60 days prior.
 - Contacts of confirmed Chlamydia cases should be offered treatment prior to the results of their investigations being known (treat then test)

Chlamydia – Doxycycline is the first line of treatment.

September 2008 exam: A swab taken in the clinic showed a Gram-negative diplococcus and treatment with IM ceftriaxone was given. his symptoms have not resolved. What is the most likely explanation?

→ Co-existent Chlamydia infection (Co-existent infection with Chlamydia is extremely common in patients with gonorrhoea).

Gonorrhoea

Epidemiology

• Gonorrhoea is the second most common bacterial STI in the UK after chlamydia.

Pathogen

- Neisseria gonorrhoeae (N. gonorrhoeae, gonococcus)
- Gram-negative, intracellular, aerobic, diplococci

Transmission

- Sexual (oral, genital, or anal)
- Perinatal

Incubation period: 2-5 days

Risk factors: multiple sexual partners in recent months, known partner with gonorrhoea, drug use, prior STI, and men who have sex with men.

Features

- Primary infection is symptomatic in 90-95% of men, but only 50% of women.
- Urogenital features
 - ⇒ males: urethral discharge, dysuria
 - ⇒ females: cervicitis e.g. leading to vaginal discharge
 - ⇒ rectal and pharyngeal infection is usually asymptomatic
- Gonorrhoeae can cause invasive infections such as pelvic inflammatory disease and Fitz-Hugh-Curtis syndrome in women and epididymitis and prostatitis in men.
 - ⇒ Fitz-Hugh-Curtis syndrome or perihepatitis. This inflammation of the Glisson capsule surrounding the liver can cause sharp pleuritic right upper quadrant pain with nausea, vomiting, and fever.
- Disseminated gonococcal infection (DGI) (haematogenous spread from mucosal infection)
 - Arthritis-dermatitis syndrome: a triad of:
 - 1) Polyarthralgias: migratory, asymmetric arthritis that may become purulent
 - 2) **Tenosynovitis**: simultaneous inflammation of several tendons
 - 3) Dermatitis: vesicular, pustular, or maculopapular lesions
 - ⇒ Purulent gonococcal arthritis (without skin lesions)
 - Abrupt inflammation in up to 4 joints (commonly knees, ankles, and wrists)
 - ⇒ Not to be confused with reactive arthritis

Diagnosis

- Test of choice: nucleic acid amplification testing (NAAT)
- Culture: All individuals with gonorrhoea diagnosed by NAAT should have cultures taken for susceptibility testing prior to treatment.

Complications

- Increased risk of acquiring HIV infection. Individuals diagnosed with gonorrhoea should be tested for all sexually transmitted infections including HIV
- local complications: urethral strictures, epididymitis and salpingitis (hence may lead to
 infertility). Gonococcal infection being the most common cause of septic arthritis in
 young adults.
- **Disseminated gonococcal infection (DGI)**, septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome).

Management (British Society for Sexual Health and HIV (BASHH) guidelines- 2018)

- First line empirical treatment is now monotherapy with ceftriaxone 1 g intramuscularly
 - ⇒ Use Ciprofloxacin 500 mg orally as a single dose as a first line when infection is known to be susceptible
 - in penicillin-allergic patients ceftriaxone and cefixime are suitable treatment options, unless there is a history of severe hypersensitivity (e.g. anaphylactic reaction) to any beta-lactam antibacterial agent (penicillins, cephalosporins, monobactams and carbapenems)
 - Cefixime 400 mg orally as a single dose plus azithromycin 2 g orally.
- A test of cure (TOC) is recommended in all cases.
 - ⇒ if symptomatic → Culture, performed at least 72 hours after completion of therapy
 - ⇒ if asymptomatic → NAAT, performed 14 days after completion of therapy followed by culture if NAAT-positive.

- Sexual partners must be treated simultaneously to avoid reinfections.
 - Who partners should be notified?
 - Male patients with symptomatic urethral infection: All partners within the preceding two weeks, or the last partner if longer than two weeks ago.
 - Patients with infection at other sites or asymptomatic infection: All partners within the preceding three months
 - ⇒ Who should be treated?
 - For those presenting <u>after</u> 14 days of exposure → treat only following a positive test for gonorrhoea
 - For those presenting within 14 days of exposure:
 - epidemiological treatment based on a clinical risk assessment
 - In asymptomatic individuals, it may be appropriate to not give epidemiological treatment, and to repeat testing 2 weeks after exposure.
- DGI → IV ceftriaxone 1 g OD for 7 days. (May be switched to oral 2 days → Cefixime 400 mg or Ciprofloxacin 500 mg twice daily)

Cephalosporins are now the treatment of choice for Gonorrhoea

Acute monoarthritis, a pustular rash and synovial fluid analysis suggestive of joint sepsis in a young woman make gonococcal arthritis the most likely diagnosis.

More commonly patients present with co-infection with Chlamydia trachomatis.

May 2014 exam: H/O a purulent urethral discharge. A sample of the discharge is shown to be a Gram-negative diplococcus. What is the most appropriate antimicrobial therapy?

→ Intramuscular ceftriaxone stat dose + oral azithromycin stat dose

January 2016 exam: What is the most likely complication from repeated *Neisseria* gonorrhoea infection?

- → Infertility
 - (Infertility secondary to pelvic inflammatory disease (PID) is the most common complication of gonorrhoea)

Toxoplasmosis

Congenital toxoplasmosis

- cerebral calcification
- chorioretinitis

Overview

- Toxoplasma gondii is an obligate intracellular protozoa which infects the body via the GI tract, lung or broken skin.
- It's oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle.

Transmission (fecal-oral route)

- Toxoplasmosis can be contracted through:
 - 1. cysts in meat, (from undercooked meat)
 - The usual animal reservoir is the cat, although other animals such as rats carry the disease.
 - Kittens are the primary host (mature cats are less likely to secrete toxoplasma)
 - sheep and cattle eat food contaminated with soil contaminated by kitten faeces; and humans ingest the organisms in poorly cooked meat.
 - Oocysts excreted with cat faeces can remain in soil for months.
 - 2. oocysts in cat feces,
 - ingestion of fresh food contaminated by toxoplasma excreted in cats' faeces.
 - 3. transplacental → Congenital toxoplasmosis.

Epidemiology

- 30% risk of <u>reactivation</u> in immunocompromised (especially CD4+ count < 100 cells/µL)
 - ⇒ in those not receiving prophylaxis or antiretroviral therapy
- ~ 30% of the worldwide population is infected

Risk factors

- HIV patients when the CD4+ count is less than 100cells/microL
 - ⇒ Toxoplasmosis is the most common central nervous system protozoal infection that presents with brain abscesses in patients with HIV.

Pathophysiology

• HIV is associated with <u>reactivation</u> of the disease.

Feature

- Most infections are asymptomatic.
- often <u>features resembling infectious mononucleosis</u> (fever, malaise, lymphadenopathy).
 - ⇒ Highly characteristic of toxoplasmosis is <u>asymmetrical lymphadenopathy</u> limited to an isolated lymph node group.
- Other less common manifestations include meningio-encephalitis and myocarditis.
- Can present with fits in patients with AIDS
 - Most common infection of the central nervous system in patients with AIDS
 - ring-enhancing lesion on head imaging
 - MRI is more sensitive and preferred
 - CD4+ count < 100 cells/µL</p>
- Eye manifestations include:

- ⇒ Focal choroido-retinitis
- ⇒ Granulomatous uveitis
- □ Optic atrophy
- ⇒ Retinal detachment
- ⇒ Cataract
- ⇒ Posterior uveitis
- ⇒ Glaucoma.
- Congenital toxoplasmosis presents with a classic triad of:
 - 1. chorioretinitis.
 - 2. hydrocephalus and
 - 3. intracranial calcifications.

Investigation

- antibody test: Serology testing for anti-toxoplasma IgM and IgG antibodies via ELISA
 - ⇒ The serologic diagnosis of toxoplasmosis in immunocompromised patients is based on the presence of <u>IgG</u> antibodies.
- · Sabin-Feldman dye test
- Congenital toxoplasmosis is associated with elevated platelet count.
- HIV patients usually presents with multiple ring-enhancing lesions on brain MRI.

Treatment

- Symptomatic patients usually have a self-limiting infection.
- Treatment usually reserved for those with severe infections or patients who are immunosuppressed
 - ⇒ pyrimethamine plus sulphadiazine for at least 6 weeks
 - Folinic acid, (also known as leucovorin), should be added to prevent pyrimethamine- associated hematologic toxicity

Prevention

- Trimethoprim-sulfamethoxazole is the therapy of choice for prophylaxis against toxoplasmosis reactivation.
- pregnant women
 - ⇒ Since the protozoal infection is commonly contracted through the handling of cat feces, pregnant women should be advised to <u>avoid contact with cat litter</u> to reduce their fetus's risk for congenital infection.
- for infected pregnant to prevent maternal-fetal transmission → spiramycin.
 - ⇒ Risk of fetopathy is reduced by more than 50% if spiramycin, which can prevent maternal-fetal transmission, is given to mothers

Pyrimethamine

- MOA → Dihydrofolate Reductase (DHFR) Inhibitor (competitive inhibitor)
 - ⇒ DHFR is a key enzyme for production of tetrahydrofolate, a cofactor that is required for the synthesis of DNA and proteins.
- Indications: used as an antimalarial or with a sulfonamide to treat toxoplasmosis.

Sulfadiazine

 Bacteriostatic, inhibits bacterial folic acid synthesis by competing with para amino benzoic acid.

Spiramycin

- Macrolide antibiotics inhibit bacterial growth by targeting the 50S ribosomal subunit
- Resistance to spiramycin is commonly attributed to mutations in 50S rRNA

January 2018 exam: HIV positive man is admitted with right-sided hemiplegia. CT scan shows multiple ring enhancing lesions. A diagnosis of cerebral toxoplasmosis is suspected. What is the most suitable management?

→ Pyrimethamine and sulphadiazine

At which CD4 count should prophylaxis against toxoplasmosis begin?

- → <100 cells/µL (with trimethoprim-sulfamethoxazole).
 - ⇒ although prophylaxis for toxoplasmosis is not required until the CD4 count is <100 cells/microL, the patient will be covered at a CD4 count <200 cells/microL when prophylaxis against *P. jiroveci* is instituted.

What is risk of transmission of HIV to a health care worker after percutaneous exposure?

- ⇒ 0.3% with no prophylaxis.
 - the risk is reduced by ~80% when post exposure prophylaxis is administered.

HIV- white lesion in oral mucosa

- Oral hairy leukoplakia are white oral lesions caused by the Epstein-Barr virus.
- a condition seen in HIV-infected patients with a CD4 count between 200 and 500/mm³.
- Unlike oral candidiasis (thrush), these lesions cannot be scraped off the tongue and buccal mucosa.

H1N1 influenza pandemic

Overview

- The H1N1 virus is a subtype of the influenza A virus
- the most common cause of flu in humans.
- Only influenza type A viruses are known to have caused pandemics.
- Influenza A and B viruses circulate and cause outbreaks and epidemics.
- The 2009 pandemic was caused by a new strain of the H1N1 virus.
- incubation period is about 2 days.
- In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

The following groups are particularly at risk:

- patients with chronic illnesses and those on immunosuppressants
- pregnant women
- · young children under 5 years old

Features: The majority of symptoms are typical of those seen in a flu-like illness:

- fever greater than 38°C
 rhinitis
- myalgia

sore throat

lethargy

cough

headache

· diarrhoea and vomiting

A minority of patients may go on to develop an acute respiratory distress syndrome which may require ventilatory support.

Treatment

There is evidence to support the use of oseltamivir as a prophylactic agent against influenza

There are two main treatments currently available:

Oseltamivir (Tamiflu)

- action
 - ⇒ neuraminidase inhibitor which prevents new viral particles from being released by infected cells, thus, slowing viral replication down rather than directly killing the virus particle.
 - This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.
- Administration
 - ⇒ oral medication
- Indications
 - ⇒ For critically ill patients with confirmed or suspected H1N1,
 - oseltamivir 150 mg bd for ten days is the recommended treatment.
 - ⇒ 1st line for influenza B
 - prophylaxis against influenza.
 - NICE guidance recommends prophylaxis with oseltamivir within 48 hours of **close contact** with a patient infected with influenza for high risk patients.
 - Zanamivir can be used within 36 hours of contact with an infected
 - zanamivir is associated with idiopathic bronchial hypersensitivity, as such it is largely considered a second line agent for treatment of
 - may be used in the prophylactic treatment of healthcare workers during flu epidemics.
 - However, viral replication is rapid and to be effective the drug must be given as early as possible after the development of symptoms of flu and preferably within 48 hours.
- side-effects
 - ⇒ common side-effects include nausea, vomiting, diarrhoea and headaches. Gastrointestinal symptoms are the most common side-effects of oseltamivir (Tamiflu).

Zanamivir (Relenza)

- action
 - ⇒ also, a neuraminidase inhibitor
- administration
 - ⇒ inhaled medication
 - ⇒ intravenous preparations are available for patients who are acutely unwell
 - The only parenteral alternative is zanamivir (300 mg IV for 10 days).
 - can be safely given using peripheral venous access.
 - For **hospitalized influenza patients** with suspected or known gastric statis. gastric malabsorption, gastrointestinal bleeding, or for patients suspected or confirmed with oseltamivir-resistant influenza virus infection, intravenous zanamivir should be considered.
- Indications
 - ⇒ Zanamivir is a second line therapy for Influenza B, but first line for Influenza A.
- Side effects
 - ⇒ may induce bronchospasm in asthmatics

Intensive Care Management of Pandemic (H1N1) Influenza

- Ideally patients should be nursed in a negative pressure room.
- NIV
 - ⇒ Whilst there is no evidence that NIV prevents invasive ventilation in H1N1 patients, it is commonly used as bridging therapy.

- ⇒ It is important to remember that these are open circuits and still require personal protection for staff.
- ⇒ NIV should be started after the mask is secured to the face
 - Ensuring that a well-fitting mask is in place before airflow starts can reduce the amount of aerosol production.
- ⇒ Experience with helmet devices is limited but increasing, and it has been successful in patients who are unable to tolerate the nasal or orofacial devices. The advantage is that it may provide a tighter seal than nasal or orofacial devices.
- avoiding water humidification and use of a closed hood is also advised.

Influenza treatment

- Oseltamivir (tamiflu) is the first line treatment recommended for patients with suspected or confirmed Influenza A.
- Zanamivir is useful in patients with poor swallow or in those with suspected or confirmed exposure to oseltamivir-resistant influenza.

Infectious mononucleosis & (Epstein-Barr virus)

Atypical lymphocytes - ?glandular fever

Aetiology

- Infectious mononucleosis (glandular fever) is caused by the Epstein-Barr virus (also known as human herpesvirus 4, HHV-4).
- The incubation period of EBV infectious mononucleosis is 1-2 months.

Epidemiology

most common in adolescents and young adults.

Pathophysiology

 The CD8+ T-cell response caused by infectious mononucleosis, leads to generalized lymphadenopathy, splenomegaly, and high WBC count with atypical lymphocytes.

Features

EBV infectious mononucleosis → triad of fever, pharyngitis, and lymphadenopathy.

- sore throat
- lymphadenopathy
 - ⇒ Bilateral posterior cervical adenopathy is most highly suggestive of EBV infectious mononucleosis.
- Pyrexia, malaise, anorexia, headache
- · palatal petechiae
 - ⇒ Palatal petechiae of the posterior oropharynx distinguish infectious mononucleosis from other causes of viral pharyngitis but do not distinguish it from group A streptococcal pharyngitis, in which palatal petechiae may occur.
- Uvular edema is an uncommon, but, if present, it is a helpful sign in distinguishing EBV infectious mononucleosis from other causes of viral pharyngitis or from group A streptococcal pharyngitis.
- splenomegaly occurs in around 50% of patients and may rarely predispose to splenic rupture
- hepatitis

- haemolytic anaemia secondary to cold agglutins (IgM)
- a maculopapular, pruritic rash develops in around 99% of patients who take ampicillin/amoxicillin whilst they have infectious mononucleosis
 - ⇒ Drug-induced rash is usually pruritic and is prolonged, in contrast to the viral rash of EBV infectious mononucleosis.
 - ⇒ Early infectious mononucleosis may present with a maculopapular generalized rash.It is nonpruritic and rapidly disappears.
- Because **leukocytosis** is the rule in infectious mononucleosis, the presence of a **normal or decreased WBC count should suggest an alternative diagnosis.**
- Lymphocytosis
 - ⇒ Relative lymphocytosis (≥ 60%) plus atypical lymphocytosis (≥ 10%) are the characteristic findings of EBV infectious mononucleosis.
- presence of 50% lymphocytes with at least 10% atypical lymphocytes
 - ⇒ Atypical lymphocytes
 - most commonly seen in patients who have infectious mononucleosis.
 - Other causes
 - drug reactions (phenytoin),
 - stress.
 - viral or bacterial infections.
 - allergies,
 - autoimmune diseases, thyroid problems
 - malignancy.
- ESR is most useful in differentiating group A streptococcal pharyngitis from EBV infectious mononucleosis.
 - ⇒ (ESR elevated with EBV infectious mononucleosis, not elevated in group A streptococcal pharyngitis).

atypical lymphocytosis point towards a viral illness

Diagnosis

- heterophile antibody test (Monospot test) (immunoglobulin IgM to EBV)
 - ⇒ the initial screening test
 - ⇒ sensitivity 85% and specificity 100%.
 - ⇒ Cytomegalovirus is a herpesvirus that causes infectious mononucleosis with a negative monospot test.
- EBV serological tests
 - ⇒ Definitive diagnosis
 - ⇒ should be obtained in patients with a mononucleosis-like illness and a negative finding on the Monospot test.

Management is supportive and includes:

- rest during the early stages, drink plenty of fluid, avoid alcohol
- · simple analgesia for any aches or pains
- consensus guidance in the UK is to avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture
- unfortunately on clinical appearances it is not possible to distinguish bacterial from viral or throat infections with any degree of reliability.

- If the child has EBV infection, then the administration of Amoxicillin will give an erythematous rash. Non-vomiting patients can be treated with oral penicillin-v.'
- Patients with EBV infectious mononucleosis who have positive throat cultures for group A streptococci should not be treated because this represents colonization rather than infection
- complicated EBV infectious mononucleosis :
 - ⇒ Short courses of corticosteroids are indicated for EBV infectious mononucleosis with:
 - hemolytic anemia,
 - thrombocytopenia,
 - CNS involvement, or
 - extreme tonsillar enlargement (impending airway obstruction).

EBV: associated malignancies:

- · Burkitt's lymphoma
- · Hodgkin's lymphoma
- nasopharyngeal carcinoma

In which structure is the immune response most likely localized? → Paracortex

- immune response to the virus takes place through T-cell mediated immune responses, which take place in the **lymphocyte-rich areas of the lymph node**, namely the **paracortex**.
- A biopsy of the lymph node of this patient would show reactive hyperplasia due to increased activity of the paracortex.

Parvovirus B19

Pathogen: Parvovirus B19 is a single-strand DNA virus.

Transmission: particularly via airborne infection

Pathology

- Primarily infects progenitor cells of erythrocytes in bone marrow and endothelial cells
- Attaches to P antigen on RBCs and endothelial cells → cell destruction

Diseases

- erythema infectiosum
 - ⇒ The most widely known clinical manifestation of parvovirus B19 is erythema infectiosum ('slapped cheek syndrome'), a mild viral illness of childhood characterised by a classic exanthema in which both cheeks appear bright red as though they had been slapped.
- Aplastic crisis in patients with hemolytic anemias (e.g. sickle cell disease, thalassemias)
- Parvovirus B19-associated arthritis
 - ⇒ most commonly in adults, particularly in women
 - ⇒ affect the small joints of the hands and feet. Knees or elbows are rarely involved.
 - ⇒ may mimic rheumatoid arthritis. Unlike rheumatoid arthritis, the post-infectious arthritis associated with parvovirus B19 does not cause permanent damage to bones or joints.

• Pure red blood cell aplasia

• The virus has a tropism for rapidly dividing erythrocyte precursors which they infect and destroy. Thus, no reticulocytes (immature erythrocytes) are available to replace aging or damaged erythrocytes as they are cleared by the reticuloendothelial system. This may not have any significant impact on otherwise healthy individuals, but can trigger an aplastic crisis - particularly in patients with haemoglobinopathies.

Leishmaniasis

Mucocutaneous ulceration following travel? - Leishmania brasiliensis

- Leishmaniasis is caused by the intracellular protozoa Leishmania, (intramacrophage protozoa)
- transmitted to humans by phlebotomine sand flies.
- There are four main clinical syndromes: cutaneous, muco-cutaneous, visceral (also known as kala-azar) and post kala-azar dermal leishmaniasis.

Cutaneous leishmaniasis

- · caused by Leishmania tropica or Leishmania mexicana
- · crusted lesion at site of bite
- present with ulcers or nodules.
- usually heal spontaneously, but slowly, in immuncompetent individuals with resultant disfiguring scars.

Mucocutaneous leishmaniasis

- caused by Leishmania braziliensis
- skin lesions may spread to involve mucosae of nose, pharynx etc
- characterised by progressively destructive ulcerations of the mucosa extending from the nose and mouth to the pharynx and larynx,
- are not self-healing.

Visceral leishmaniasis (kala-azar)

- mostly caused by Leishmania donovani
- caused by the Leishmania donovani complex
 - > (L. donovani sensu stricto in East Africa and India,
 - L. infantum in Europe, North Africa and Latin America).
- incubation period of 2-6 months
- patients present with persistent systemic infection (fever, sweating, rigor, malaise, loss of appetite and weight loss) (*occasionally patients may report increased appetite with paradoxical weight loss)
- parasitic infection of the blood and reticulo-endothelial system → lymphadenopathy, massive splenomegaly and hepatomegaly
- grey skin 'kala-azar' means black sickness
- investigations
 - pancytopaenia secondary to hypersplenism
 - > There is also often marked polyclonal hypergammaglobulinaemia.
 - Visualisation of the parasite (amastigote form) from lymph nodes, bone marrow or spleen is used as a confirmatory test.
 - > PCR can be used to detect the parasite in the blood.

Anti-leishmanial antibodies can be detected, but they remain positive up to several years after cure and therefore cannot be used to detect relapse.

Treatment

- First line antimonials are sodium stibogluconate and meglumine antimoniate. Adverse effects influde cardiac arrhythmias and acute pancreatitis.
- > Amphotericin B is increasingly being used.

Post kala-azar dermal leishmaniasis

- a complication of visceral leishmaniasis
- characterised by a macular, maculo-papular or nodular rash
- frequently observed after treatment.It can also occur in immunosuppressed individuals.
- highly infectious.

Leptospirosis (Also known as Weil's disease*)

Leptospirosis - give penicillin or doxycycline

- *the term Weil's disease is sometimes reserved for the most severe form.
 - If the infection causes jaundice, kidney failure and bleeding, it is then known as Weil's disease.
 - > If it affects the lung and causes pulmonary haemorrhage, then it is known as severe pulmonary haemorrhage syndrome.
- leptospirosis is commonly seen in questions referring to sewage workers, **farmers**, vets or people who work in abattoir.
- It is caused by the spirochaete Leptospira interrogans (serogroup Licterohaemorrhagiae),
- classically being spread by contact with infected rat urine.
- Weil's disease should always be considered in high-risk patients with hepato-renal failure

Features

- fever
- flu-like symptoms
- renal failure (seen in 50% of patients)
- jaundice
- headache, may herald the onset of meningitis
- · subconjunctival haemorrhage
- · Haemorrhagic tendencies with purpura or petechiae
- Enlargement of liver and spleen.
- Presentation with heart failure is uncommon but has been described in severe leptospirosis.

Management

- high-dose benzylpenicillin or doxycycline
- other options: cefotaxime or ceftriaxone.

Lyme disease

Aetiology

- Lyme disease is caused by the spirochaete Borrelia burgdorferi and is spread by ticks of the genus lxodes
 - ⇒ Ixodes ricinus is predominantly responsible for its transmission in Europe.
 - ⇒ *Ixodes pacificus* and *Ixodes scapularis* are the ticks responsible for transmission of in the USA.

Features

Bilateral facial weakness can occur with Lyme disease, myasthenia gravis, sarcoidosis and bilateral Bell's palsy.

Early features

- erythema chronicum migrans (small papule often at site of the tick bite which develops into a larger annular lesion with central clearing, 'bulls-eye'. Occurs in 70% of patients)
 - ⇒ Erythema migrans is often the presenting sign of Lyme disease
- systemic symptoms: malaise, fever, arthralgia

Later features

- · CVS: heart block, myocarditis
- neurological: (Neuroborreliosis): cranial nerve palsies, meningitis
- polyarthritis

Investigation

- serology: antibodies to Borrelia burgdorferi (ELISA test for antibodies to Borrelia burgdorferi)
 - Serological tests are the most appropriate first line investigation for diagnosing Lyme disease.
 - > ELISA tests are preferred to Western blots as they are more sensitive.

Management

- Early disease:
 - ➢ doxycycline is the drug of choice for 2 − 3 weeks
 - Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
- · Disseminated disease:
 - > ceftriaxone if disseminated disease
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

MRCPUK-part-1-September 2013 exam: H/O returning from a camping holiday in the New Forest. C/O lethargy, arthralgia, rash consistent with erythema chronicum migrans. What is the most appropriate test to perform given the likely diagnosis?

→ ELISA test for antibodies to Borrelia burgdorferi

Lymphadenopathy

There are many causes of generalised lymphadenopathy

Infective

- · infectious mononucleosis
- · HIV, including seroconversion illness
- · eczema with secondary infection
- rubella
- toxoplasmosis
- CMV
- tuberculosis
- roseola infantum

Neoplastic

- leukaemia
- lymphoma

Others

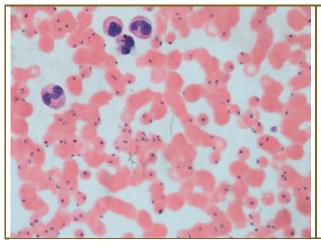
- · autoimmune conditions: SLE, rheumatoid arthritis
- · graft versus host disease
- sarcoidosis
- drugs: phenytoin and to a lesser extent allopurinol, isoniazid

Malaria

Malaria: Falciparum

Severe falciparum malaria - intravenous artesunate

 P. falciparum typically presents within the first three months of return from an endemic area.



In the slide shown, the blood film shows ring forms within erythrocytes; some erythrocytes contain two to three parasites per cell - typical of falciparum; other forms of malaria seldom have more than one parasite per red cell.

Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 C
- severe anaemia
- · complications as below
- Complications
 - > cerebral malaria: seizures, coma
 - acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
 - ➤ acute respiratory distress syndrome (ARDS) → (Respiratory rate 30 per minute)
 - hypoglycaemia
 - disseminated intravascular coagulation (DIC)

Uncomplicated falciparum malaria

- · strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

Severe falciparum malaria

- a parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state
- Hyperparasitemia, where more than 5% of the red blood cells are infected by malaria parasites
 - In 2010, WHO defined hyperparasitemia as >2%/100 000/μL in low intensity transmission areas or >5% or 250 000/μL in areas of high stable malaria transmission intensity.
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
 - I.V quinine is reserved for severe or cerebral malaria (most deaths from M. falciparum occur in first 96 hours of starting treatment).
 - The initial dose should NOT be reduced in those severely ill with renal/hepatic impairment.
 - High doses of quinine in pregnancy are teratogenic in the first trimester. However in malaria, the benefit of treatment outweighs the risk.
 - WHO Guidelines (2006) recommend artemisinins are first line in the second and third trimester. In the first trimester, both artesunate and quinine are considered treatment options.
 - Hypoglycaemia is an important side effect of quinine
 - Quinine → ↑ insulin secretion and the sensitivity of cells to insulin → hypoglycaemia
 - Malaria itself can cause hypoglycaemia too, so blood glucose should be monitored every 2 h.
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia malaria rarely causes haemodynamic collapse

Malaria: non-falciparum

Non-falciparum malarias are almost always chloroquine sensitive

P. vivax:

- The most common cause of non-falciparum malaria is *Plasmodium vivax*, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases.
- The incubation period of P. vivax can go up to six months or more with malaria being caused by hypnozoites.
 - P. falciparum incubation is normally around six days though it can go till 14 days or more.
- ➤ The Duffy antigen on RBCs acts as a receptor for P. vivax. → facilitate the entry of P. vivax in to RBCs.
 - Duffy negative individuals are therefore resistant to this strain
 - West Africans lack the Duffy blood group and therefore P. ovale replaces P. vivax in this region.

P. ovale:

- > it is quite rare
- > The incubation period is similar to that of P. vivax but on the thick film the parasites are more compact and smaller. On the thin film the red blood cells appear oval with ragged ends.

P. malariae:

- it is rare.
- Its incubation could go up to 14 days like P. falciparum.
- The thick film will show a few compact rings or small neat schizonts or small round gametocytes with yellow-brown pigment. The thin film will show red blood cells in band forms.
- Plasmodium vivax is often found in Central America and the Indian Subcontinent whilst Plasmodium ovale typically comes from Africa
- Both P. vivax and P. ovale have a liver hypnozoite stage which can cause repeated relapses.
 - > May present **six months** after return from an endemic area

Features

- fever.
 - Plasmodium vivax/ovale: cyclical fever every 48 hours.
 - > Plasmodium malariae: cyclical fever every 72 hours
- headache.
- splenomegaly
- Plasmodium malariae: is associated with nephrotic syndrome

Investigations

- · Plasmodium ovale,
 - all stages of the parasite and not just trophozoites and gametocytes are visible in the peripheral blood.
- In P. falciparum malaria, only trophozoite-ring forms and gametocytes are usually seen.

Treatment

- non-falciparum malarias are almost always chloroquine sensitive
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse.
 - all individuals should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency, as primaguine may cause haemolysis in those without the enzyme.

fast-acting	intermediate-acting	slow-acting
high-efficacy blood		low-efficacy schizonticides that
schizonticides that may be		normally need to be
effective as monotherapy		administered in combination.
Artemesinin	Quinine	Pyrimethamine
Mepacrine	Mefloquine	Doxycycline is also a very
		slow-acting antimalarial.

Pyrimethamine

- used in the treatment of uncomplicated malaria, particularly for chloroquine-resistant P.
- It acts on both the erythrocytic and hepatic phases of infection.
- · It inhibits dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, and thereby halting the processes of DNA replication, cell division and reproduction.
- It is normally used alongside a sulfonamide.

Malaria: prophylaxis

- around 75% of malaria in patients returning from endemic countries are caused by the potentially fatal Plasmodium falciparum protozoa.
- The majority of patients who develop malaria did not take prophylaxis.
- It should also be remembered that UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

Drug	Side-effects + notes	Time to begin before travel	Time to end after travel
Atovaquone + proguanil (Malarone)	GI upset	1 - 2 days	7 days
Chloroquine	Headache Contraindicated in epilepsy Taken weekly	1 week	4 weeks
Doxycycline	Photosensitivity Oesophagitis	1 - 2 days	4 weeks
Mefloquine (Lariam)	Dizziness Neuropsychiatric disturbance Contraindicated in epilepsy and mental illnesses Taken weekly	2 - 3 weeks	4 weeks
Proguanil (Paludrine)		1 week	4 weeks
Proguanil + chloroquine	See above	1 week	4 weeks

Which drug?

- In certain parts of South-East Asia there is widespread chloroquine resistance. Chemoprophylaxis using atovaquone + proguanil (Malarone), mefloquine (Lariam) or doxycycline is therefore recommended.
- > Doxycycline prophylaxis is the safest option with less resistance in many parts of the world compared to the other options available.
- Atovaquone and proguanil are used for prophylaxis especially where there are high levels of resistance against most of the other drugs.
- Proguanil should not be used alone as malaria could develop resistance to it.

Pregnant women

- Pregnant women should be advised to avoid travelling to regions where malaria is endemic. Diagnosis can also be difficult as parasites may not be detectable in the blood film due to placental sequestration. However, if travel cannot be avoided:
 - chloroquine can be taken
 - proguanil: folate supplementation (5mg od) should be given
 - Malarone (atovaquone + proguanil): the BNF advises to avoid these drugs unless essential. If taken then folate supplementation should be given
 - mefloquine: caution advised
 - doxycycline is contraindicated

Children

- It is again advisable to avoid travel to malaria endemic regions with children if avoidable. However, if travel is essential then children should take malarial prophylaxis as they are more at risk of serious complications.
 - diethyltoluamide (DEET) 20-50% can be used in children over 2 months of age
 - doxycycline is only licensed in the UK for children over the age of 12 years

MRCPUK-part-1-May 2013 exam: H/O vivax malaria treated initially with chloroquine then later given primaquine. What is the benefit of the primaquine?

→ Destroy liver hypnozoites and prevent relapse

MRCPUK-part-1-May 2014 exam: A 25-year-old man with a history of epilepsy presents for advice regarding malarial prophylaxis. Next month he plans to travel to Vietnam. What is the most appropriate medication to prevent him developing malaria?

→ Atovaguone + proguanil

Measles

Overview

- RNA paramyxovirus
- spread by droplets
- infective from prodrome until 4 days after rash starts
- incubation period = 10-14 days

Features

- prodrome: irritable, conjunctivitis, fever
 - > Patients present with the three C's: cough, coryza, and conjunctivitis.
 - Rash usually develops on the head and torso, typically sparing the wrists and hands.
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
 - Koplik's spots are small, irregular, bright red spots with blue-white centres, occurring on the inside of the cheek next to the premolars. Seen only in measles, they are diagnostic.

- > The spots usually occur briefly after the fever begins and a couple of days before the generalised rash appears.
- Not infrequently, the spots disappear as the eruption develops.
- rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent



Koplik spots

Complications

- encephalitis: typically occurs 1-2 weeks following the onset of the illness)
- subacute sclerosing panencephalitis: very rare, may present 5-10 years following the illness
- · febrile convulsions
- giant cell pneumonia
- · keratoconjunctivitis, corneal ulceration
- diarrhoea
- increased incidence of appendicitis
- myocarditis



The rash typically starts behind the ears and then spreads to the whole body

Management of contacts

- if a child not immunized against measles comes into contact with measles then MMR should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection)
- this should be given within 72 hours

Rubella

- also known as german measles.
- RNA virus , part of the togavirus family
 - > rubella has positive single-stranded RNA.
 - rubeola virus (measles) contains negative single-stranded RNA
- affects unimmunized children and presents with a rash that begins at the head and moves down with postauricular lymphadenopathy.
- A positive rubella haemagglutination inhibition (HAI) combined with a negative rubella IgM is consistent with:
 - 1. Early acute infection with rubella
 - The IgM may take several days to rise and the test should be repeated one to two weeks later.
 - 2. Previous vaccination, or
 - 3. Previous rubella infection.

Parotitis

Causes

- Bacterial parotitis
 - Commonly unilateral
 - > more common in older patients.
 - The most common bacterial cause of parotitis is *Staphylococcus aureus*.
 - ➤ The risk is increased by agents that have an atropine-like action, including medications prescribed to reduce excess respiratory secretions.
 - ➤ A ductal stone, with consequent pooling of infected secretions, should be excluded, and ultrasound is an appropriate investigation to perform for this.
 - > Antibiotics should be selected that cover typical mouth flora.
- Viral parotitis
 - Mumps parotitis is usually bilateral
 - Parotitis, orchitis, aseptic meningitis, and pancreatitis are symptoms of mumps virus infection.
- autoimmune disease, Sjogren's syndrome.
- Bulimia nervosa

Parotid swelling

- causes of bilateral parotid swelling include:
 - ⇒ Infection with viruses, including mumps, parainfluenza virus type 3, Coxsackie viruses and influenza A virus
 - ⇒ Metabolic diseases, such as:
 - diabetes mellitus
 - uraemia

- ⇒ Drugs, such as:
 - phenylbutazone
 - thiouracil
- Other conditions associated with chronic parotid swelling include:
 - ⇒ Alcoholic liver disease
 - ⇒ Sarcoidosis
 - ⇒ Sjögren syndrome
 - ⇒ Lymphoma
 - ⇒ Infection with HIV

Orf

Orf is generally a condition found in sheep and goats although it can be transmitted to humans. It is caused by the **parapox virus**.

In animals

· 'scabby' lesions around the mouth and nose

In humans

- generally affects the hands and arms
- initially small, raised, red-blue papules
- later may increase in size to 2-3 cm and become flat-topped and haemorrhagic

Pelvic inflammatory disease(PID)

Definition

- infection and inflammation of the female pelvic organs including the uterus, fallopian tubes, ovaries and the surrounding peritoneum.
- It is usually the result of ascending infection from the endocervix

Causative organisms

- Chlamydia trachomatis the most common cause
- Neisseria gonorrhoeae
- Mycoplasma genitalium
- Mycoplasma hominis
 - ⇒ one of the most frequently isolated mycoplasma in the genital tract.
 - ⇒ It is an opportunistic pathogen which may cause pelvic inflammatory disease in immunocompromised patients.
 - ⇒ Clindamycin is used in the treatment

Features

- lower abdominal pain
- fever
- deep dyspareunia
- · dysuria and menstrual irregularities may occur
- · vaginal or cervical discharge
- cervical excitation

Investigation

· screen for Chlamydia and Gonorrhoea

Management

- due to the difficulty in making an accurate diagnosis, and the potential complications
 of untreated PID, consensus guidelines recommend having a low threshold for
 treatment
- Consensus guidelines recommend treatment once a diagnosis of pelvic inflammatory disease is suspected, rather than waiting for the results of swabs
- oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline
 + oral metronidazole
- RCOG guidelines suggest that in mild cases of PID intrauterine contraceptive
 devices may be left in. The more recent BASHH guidelines suggest that the
 evidence is limited but that 'Removal of the IUD should be considered and may be
 associated with better short term clinical outcomes'

Complications

- infertility the risk may be as high as 10-20% after a single episode
- chronic pelvic pain
- ectopic pregnancy
- Fitz-Hugh-Curtis syndrome
 - ⇒ is a rare complication of pelvic inflammatory disease, resulting in liver capsule inflammation
 - ⇒ It is most often caused by untreated sexually transmitted infections including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.
 - ⇒ a patient may present with septic shock secondary to the untreated liver capsule infection.

Psittacosis (ornithosis)

- *Chlamydia psittaci* is endemic in birds including psittacine birds, canaries, finches, pigeons and poultry.
- Pet owners, vets and zoo keepers are most at risk. It is rare in children.
- Person to person transmission occurs especially in a hospital environment.
- Sputum Gram stain reveals a few leucocytes and no predominant bacteria.
- There are few signs and few laboratory/x ray findings.
- Positive serology is with complement-fixing antibodies.
- It is treated with tetracycline.

Pyogenic liver abscess

• The most common organisms found in pyogenic liver abscesses are *Staphylococcus* aureus in children and *Escherichia coli* in adults.

Management

- amoxicillin + ciprofloxacin + metronidazole
- if penicillin allergic: ciprofloxacin + clindamycin

January 2018 exam: What is the most appropriate antibiotic therapy to accompany drainage of liver abscess?

→ Amoxicillin + ciprofloxacin + metronidazole

Pyrexia of unknown origin

indium labelled leukocyte study:

 useful for detecting occult abscesses in patients with pyrexia of unknown origin where conventional scans have failed to detect a source of infection.

Definition

 Defined as a prolonged fever of > 3 weeks which resists diagnosis after a week in hospital Neoplasia

- lymphoma
- hypernephroma
- preleukaemia
- · atrial myxoma

Infections

- abscess
- TB

Connective tissue disorders

Q fever

Q fever - Coxiella burnetti

Overview

- Q fever is a zoonotic disease caused by <u>Coxiella burnetii</u> an obligate <u>gram-negative</u> intracellular bacterium.
- The organism is very resistant to drying.
- does not grow on standard culture media.

Transmission

- The organism is usually inhaled from infected dust (animal products)
- · acquired through contact with animals.
 - ⇒ Cattle, sheep and goats are the primary reservoirs of *C. burnetii*.
- drinking unpasteurised milk from infected cows.

Risk factors

 It is not notifiable, but can occur in outbreaks in farming communities and in abattoirs. and therefore an occupational history is very important.

Features:

- · high fevers, chills, sweats
- severe headache, (typically retrobulbar)
- · general malaise, myalgia,
- · confusion,
- sore throat, ,
- non-productive cough,
- nausea, vomiting, diarrhoea, abdominal pain
- chest pain.
- Between 30% and 50% of patients with a symptomatic infection will develop pneumonia.
- may be complicated by immune complex-mediated glomerulonephritis

- Chronic infection can manifest as hepatitis, osteomyelitis or endocarditis.
- In Q fever endocarditis:
 - ⇒ the aortic valve is involved in over 80% of cases.
 - ⇒ A murmur is not always present, but augmentation of an existing murmur may occur.
 - ⇒ Low-grade fever (or no fever).
 - ⇒ signs of heart failure,
 - ⇒ hepatosplenomegaly,
 - ⇒ clubbing,
 - ⇒ arterial emboli,
 - ⇒ leukocytoclastic vasculitic rash.

Diagnosis:

- Confirmed by serological testing for C. burnetii.
 - ⇒ phase I antibody titre to Coxiella burnetti (IgG and/or IgA) greater than 1:200 is virtually diagnostic of Q fever.
- chest X-ray might show multilobar consolidation.
- Anaemia
- Thrombocytopenia
- Elevated ESR
- Hypergammaglobulinaemia
- liver function tests
 - ⇒ abnormal in the majority of patients and some will develop hepatitis.
- Microscopic haematuria may be present.

Treatment:

- Most patients will recover within a few months with no treatment.
- Doxycycline is the treatment of choice for acute Q fever. OR prolonged courses of tetracyclines.

Prognosis

- Only 1–2% of people with acute Q fever die of the disease.
- · Chronic Q fever
 - Endocarditis with negative culture findings and seropositivity is the main clinical presentation of chronic Q fever,
 - usually occurring in patients with preexisting cardiac disease including valve defects, rheumatic heart disease, and prosthetic valves.

Rabies

Rabies - following possible exposure give immunglobulin + vaccination

Overview

- Rabies is a viral disease that causes an acute encephalitis.
- The rabies virus is classed as a RNA rhabdovirus and has a bullet shaped capsid.
- It is commonly transmitted by bat, raccoon and skunk bites.
- Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Features

- · prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries.

Following an animal bite in at risk countries:

- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination
- Lyssaviruses such as rabies cannot cross intact skin and humans are regarded as an end-host (outside of transplantation-associated transmission). Therefore, only standard infection-prevention precautions such as gloves and gowns are required.

Scabies

<u>Scabies</u> should be suspected in any sexually active young person who presents with generalised pruritus without any specific signs.

Overview

- Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact.
- It typically affects children and young adults.

Pathophysiology

- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

Features

- · widespread pruritus
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
 - ⇒ The tiny erythematous burrows in the web spaces of the fingers are almost pathognomonic
- in infants the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

Investigation

• **Skin scrapings** → demonstrate *Sarcoptes scabiei*

Management

- first-line is → permethrin 5%
- second-line is → malathion 0.5%
- Application should be repeated seven days after initial treatment to kill any mites hatched from eggs in that time
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)

- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
 - ⇒ Re-infection most likely means → Other household members were not treated

 launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

Patients should be given the following instructions:

- The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation.
- apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and leave on the skin for 8-12 hours for permethrin, or for 24 hours for malathion, before washing off
- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- · repeat treatment 7 days later

Crusted (Norwegian) scabies

- Crusted scabies is seen in patients with suppressed immunity, especially HIV.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- Ivermectin is the treatment of choice and isolation is essential



Helminths
Nematodes (roundworms)

Worm	Notes	Treatment
Strongyloides stercoralis	Larvae are present in soil and gain access to the body by penetrating the skin Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered	Ivermectin and - bendazoles are used
Enterobius vermicularis (pinworm)	asymptomatic in 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	-bendazoles
Ancylostoma duodenale, Ne cator americanus(h ookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova	-bendazoles
Loa loa	Transmission by deer fly and mango fly	Diethylcarbamazine
	Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae	
Trichinella spiralis	Typically develops after eating raw pork. Features include fever, periorbital oedema and myositis (larvae encyst in muscle)	-bendazoles
Onchocerca volvulus	Causes 'river blindness'. Spread by female blackflies	Ivermectin
remande	Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria	= IVERmectin
Wuchereria bancrofti	Transmission by female mosquito	Diethylcarbamazine
bancroiti	Causes blockage of lymphatics → elephantiasis	
Toxocara canis (dog	Transmitted through ingestion of infective eggs.	Diethylcarbamazine
roundworm)	Features include visceral larva migrans and retinal granulomas VISCious dogs → blindness	

Worm	Notes	Treatment
Ascaris lumbricoides(giant roundworm)	 the most common nematode parasite of humans. Eggs are visible in faeces large roundworm, growing up to 35 cm in length result of pneumonitis caused by the worm's migration through the lungs May cause intestinal obstruction and occasional migrate to lung (Loffler's syndrome) biliary/pancreatic duct obstruction. 	-bendazoles Piperazine is the treatment of choice in patients presenting with bowel obstruction; mebendazole may be used to treat other infections.

Cestodes (tapeworms)

Worm	Notes	Treatment
Echinococcus granulosus	 Responsible for hydatid disease Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers. Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal) the most appropriate next step in diagnosis? → ELISA testing for Echinococcus 	 bendazoles alone (For smaller cysts) albendazole combined with surgical excision. (for larger cysts)
Taenia solium	Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
Fasciola hepatica (the liver fluke)	May cause biliary obstruction	Triclabendazole

Trematodes (flukes)

Worm	Notes	Treatment
Schistosoma haematobium	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
Paragonimus westermani	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs	Praziquantel
Clonorchis sinensis	Caused by undercooked fish Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	Praziquantel

Schistosomiasis

Schistosoma haematobium causes haematuria

Schistosomiasis, or bilharzia, is a parasitic flatworm infection.

Types

- Schistosoma mansoni and Schistosoma intercalatum: intestinal schistosomiasis
- Schistosoma haematobium: urinary schistosomiasis
 - ⇒ This typically presents as a 'swimmer's itch' in patients who have recently returned from Africa. Schistosoma haematobium is a risk factor for squamous cell bladder cancer

Features

- frequency
- haematuria
- bladder calcification

Management

- · single oral dose of praziquantel
- Praziquantel is the treatment of choice for all Schistosoma species.
- CNS involvement
 - ⇒ S. japonicum
 - Praziquantel 60 mg/kg per day for 6 days and prednisolone 1 mg/kg per day
 - Praziquantel 60 mg/kg per day for six days is recommend for S. japonicum with a maximum dose of 5 grams per day with prednisolone 1 mg/kg.
 - ⇒ S. mansoni and S. haematobium.
 - Praziquantel 40 mg/kg per day for three days is recommended for S. mansoni and S. haematobium.
 - Since some of the pathology in neuroschistosomiasis is secondary to hypersensitivity reactions there is need to use a steroid, in this case prednisolone 1 mg/kg per day. There is no consensus about when it should be started or stopped.

Complications:

- S. mansoni Eggs can migrate to liver through the portal venous system where they can
 elicit a granulomatous fibrosing reaction → venous blockade → Portal venous hypertension
 → varicies and upper GIT bleeding.
- **S.** haematobium leads to granulomatous inflammation, ulceration of the vesicle and ureteral walls. Subsequent fibrosis can cause bladder neck obstruction, hydroureter and hydronephrosis. These changes can cause a chronic renal impairment and predispose to secondary bacterial infection as well as squamous cell carcinoma.
- all schistosome species can result in immune complex deposition in the kidneys leading to a proteinuria and nephrotic syndrome.
- S. japonicum:
 - ⇒ is prevalent in China, Indonesia, Thailand and the Philippines mainly.
 - ⇒ It is the commonest cause of Schistosoma encephalitis.
 - ⇒ Its eggs are smaller unlike those of *S. masoni and S. haematobium*which are more likely to cause spinal cord schistosomiasis because of their larger size and spikes which do not enable them get to the brain hence the infection in the spinal cord.

Strongyloides stercoralis

• Strongyloides stercoralis is a human parasitic nematode worm. The larvae are present in soil and gain access to the body by penetrating the skin. Infection with Strongyloides stercoralis causes strongyloidiasis.

Features

- diarrhoea
- abdominal pain/bloating
- papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

Treatment

ivermectin and albendazole are used

Tape worms

• Tape worms are made up of repeated segments called proglottids. These are often present in faeces and are useful diagnostically

Cysticercosis

- caused by Taenia solium (from pork) and Taenia saginata (from beef)
- These may affect any tissue in the body but are commonest in subcutaneous tissues and (CNS) → patient with a palpable nodule who has an epileptic seizure
- · management: niclosamide

Hydatid disease

- caused by the dog tapeworm Echinococcus granulosus
- · life-cycle involves dogs ingesting hydatid cysts from sheep liver
- often seen in farmers
- · may cause liver cysts
- management: albendazole

Trypanosomiasis

- Two main form of this protozoal disease are recognised:
 - 1. African trypanosomiasis (sleeping sickness) and
 - 2. American trypanosomiasis (Chagas' disease)

1. African trypanosomiasis, or sleeping sickness

- Two forms of African trypanosomiasis, or sleeping sickness, are seen:
 - 1) Trypanosoma brucei gambiense in West Africa
 - West African trypanosomiasis has a slower course. Symptoms start several weeks or even months after the tsetse fly bite.
 - 2) Trypanosoma brucei rhodesiense in East Africa.
 - Trypanosoma rhodesiense tends to follow a more acute course.
 - progression is more rapid starting within days of infection. Death may occur within weeks or months.
 - Rash is a more prominent feature and lymphadenopathy is less frequently present.
- Both types are spread by the tsetse fly.
- Clinical features include:
 - Trypanosoma chancre painless subcutaneous nodule at site of infection

- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis
- The reversal of the sleep wake cycle is typical and can be accompanied by behavioural changes.

Stages

- The first stage of disease is haematolymphatic spread and is accompanied by fever, and lymphadenopathy (discrete, rubbery, non-tender nodes). A rash sometimes occurs and mild hepatosplenomegaly may develop.
- The second stage is the meningoencephalitic stage. This occurs months or years after the acquisition of infection. Manifestations include personality change and progressive indifference with daytime somnolence.

Extrapyramidal signs and ataxia are common.

- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

2. American trypanosomiasis, or Chagas' disease

- caused by the protozoan Trypanosoma cruzi.
- Transmitted by triatomine bug bite.
- > Features:
 - acute phase:
 - asymptomatic (95%)
 - chagoma (an erythematous nodule at site of infection)
 - periorbital oedema
 - Chronic Chagas' disease mainly affects the heart, gastrointestinal tract and CNS.
 - ❖ Cardiac feature → myocarditis may lead to dilated cardiomyopathy (with apical atophy) and arrhythmias.
 - → Cardiac involvement is the leading cause of death in patients with Chagas' disease
 - GIT feature:
 - → Mega-oesophagus (causing dysphagia)
 - → Mega-colon (causing constipation)
 - ❖ CNS feature → meningoencephalitis

> Management

- treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure.

Nematodes

- most common cause of <u>cutaneous</u> larva migrans → Ancylostoma braziliense
- commonest cause of <u>visceral</u> larva migrans → Toxocara canis

Ancylostoma braziliense

- most common cause of cutaneous larva migrans
- common in Central and Southern America
- The infection is acquired by direct contact with dog or cat faeces often acquired when sunbathing on contaminated sand, etc. The larvae burrow in the dermo-epidermal junction.
- **Symptoms** include pruritus and a raised, serpiginous erythematous rash that migrates at a rate of up to 1 cm/day.
- Treatment i
 - ⇒ The disease is self-limiting but the duration of disease varies considerably
 - ⇒ Oral ivermectin in a single dose of 200 μg/kg body weight is the main treatment.
 - ⇒ Other treatment options include oral albendazole or topical thiabendazole.

Strongyloides stercoralis

- acquired percutaneously (e.g. walking barefoot)
- causes pruritus and larva currens this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate
- abdo pain, diarrhoea, pneumonitis
- may cause Gram negative septicaemia due carrying of bacteria into bloodstream
- eosinophilia sometimes seen
- management: thiabendazole, albendazole. Ivermectin also used, particularly in chronic infections

Toxocara canis

- commonly acquired by ingesting eggs from soil contaminated by dog faeces
- commonest cause of visceral larva migrans
- other features: eye granulomas, liver/lung involvement



cutaneous larva migrans



cutaneous larva migrans

Filariasis

- Manifestations of filariasis
 - ⇒ Remember 3 L's:
 - Lymphatic filariasis (caused by Wuchereria bancrofti and Brugia malayi)
 - Loiasis (caused by Loa loa)
 - Light (light, sight, blindness river blindness caused by Onchocerca volvulus)

⇒ Tropical eosinophilia:

- Tropical eosinophilia is an allergic reaction to microfilaria of Wuchereria bancrofti.
- Characteristic features include:
 - myalgia; fatigue;
 - weight loss;
 - cough and dyspnoea with wheeze;
 - fever;
 - current or previous residence in an area endemic for filariasis (southern Asia, Africa, India, South America);
 - !ymphadenopathy;
 - marked peripheral blood eosinophilia
 - high titres of anti-filarial antibodies.
- The chest x ray shows bilateral reticulonodular shadowing.
- This condition is commonly accompanied by false positive serological tests for syphilis and high titres of cold agglutinins.
- There is typically a rapid response to treatment with diethylcarbamazine.

Diagnosis

- ⇒ finger prick test
 - identifying microfilariae on Giemsa stained, thin and thick blood film smears.
- ⇒ "Filariasis fills the blood at night."
- ⇒ To remember that Microfilaria can be demonstrated in peripheral smear only at night.
 - W. bancrofti, whose vector is a mosquito; night is the preferred time for blood collection.
 - Loa loa's vector is the deer fly; daytime collection is preferred.
- Which immune mechanisms does the body employ against the live filarial worms?
 - → Antibody-dependent cell-mediated cytotoxicity

Loiasis

- Loiasis is a filarial infection caused by Loa Loa.
- It is transmitted by the Chrysops deerfly and tends to occur in rainforest regions of Western and Central Africa.
- It has less pathological features than other the microfilarial infections Onchocerciasis and Lymphatic Filariasis.

Clinical features

- pruritus
- urticaria
- Calabar swellings: transient, non-erythematous, hot swelling of soft-tissue around joints
- 'eye worm' the dramatic presentation of subconjuctival migration of the adult worm.

Treatment

- Ivermectin is currently the drug of choice for control of both Onchocerciasis and Lymphatic Filariasis in Africa.
- high loa loa microfilaraemia is associated with encephalopathy following treatment with either Ivermectin or DEC. This occurs due to the death of vast numbers of blood microfilaria. Both of these drugs are contraindicated if loa loa microfilaraemia exceeds 2500 mf/ml.



Adult Loa loa parasite. Loa loa is the filarial nematode (roundworm) species that causes loa loa filariasis. It is commonly known as the 'eye worm.' Its geographic distribution includes Africa and India. Credit: NIAID

Animal bites

Animal bite - co-amoxiclay

- The majority of bites seen in everyday practice involve dogs and cats.
- Dog bites become infected in 10% of cases.
- the most common isolated organism is Pasteurella multocida.

Management

- cleanse wound
- · current BNF recommendation is co-amoxiclay
- if penicillin-allergic then doxycycline + metronidazole is recommended



MRCPUK-part-1-January- 2019: H/O a dog bite to right hand. What is the most appropriate antibiotic therapy? Co-amoxiclav

MRCPUK-part-1-January- 2018: A patient has been bitten by his dog that morning. the wound looks clean as he has washed it well. He is penicillin allergic. Which antibiotic therapy is suitable?

→ Metronidazole and doxycycline in combination

Rocky Mountain spotted fever

- Rocky Mountain spotted fever (RMSF) is a systemic vasculitis caused by infection with Rickettsia rickettsii, a tick-borne, gram-negative, intracellular bacterium, that primarily infects vascular endothelial cells.
- It is the most common fatal tick-borne infection in the USA
- Transmitted by bites of the dog or wood tick, which predominantly occur in spring and summer throughout much of the United States.

Feature

- Fever, headache, myalgia, rash, vomiting, and history of tick bite are commonly reported; however, the absence of any of these does not exclude diagnosis. A history of tick bite may not be elicited in up to 45% of cases.
- The rash usually sparing the face and may involve palms and soles.
- Signs and symptoms may be difficult to distinguish from those of common viral illnesses, leading to delayed diagnosis.
- Diagnosis should be considered in any person with a compatible clinical presentation and recent outdoor exposure.
- Late-stage manifestations, such as noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]) and cerebral edema, are consequences of microvascular leakage.

Investigation

• PCR (polymerase chain reaction) is the most appropriate test

Treatment

- Doxycycline is the drug of choice for adults and children and is almost always curative, especially if given in the first 5 days of illness.
 - ⇒ Tetracyclines acts on 30S ribosomes to prevent protein synthesis in the infecting organism.

- Aluminium hydroxide can complex with this antibiotic in the gastrointestinal tract, preventing absorption. Dairy products ingested at the same time can also cause this.
- Aluminium hydroxide medication should be stoped till the antibiotic course is finished
- Because the risk of death rises if appropriate therapy is not started before the fifth day of
 illness, doxycycline should be prescribed for suspected Rocky Mountain spotted fever
 before confirmatory diagnostic test results are available.

Typhus (Rickettsial infection)

- caused by Rickettsia typhi (endemic typhus) or Rickettsia prowazekii (epidemic typhus). T
- Rickettsia prowazekii (epidemic typhus) is transmitted via human-to-human contact through body lice.
- Arthropod vectors transmit the etiologic agents to humans.
- Presented with fever and rash
- Both forms of typhus consist of a rash that classically begins centrally, and spreads outwardly sparing the palms and soles (unlike Rocky Mountain spotted fever)
- Rocky Mountain Spotted Fever can be distinguished from typhus because its rash begins peripherally, and spreads centrally to the palms, soles, and trunk.
- Doxycycline is the drug of choice for treatment in patients of all ages.

Histoplasmosis

Overview

- Histoplasmosis is one of the most common systemic fungal infections in the United States. It is endemic to the Ohio and Mississippi river valleys
- often associated with spelunkers (cave divers) or patients recently exposed to bird and bat droppings.

Feature

- The majority are asymptomatic.
- can closely mimic tuberculosis in symptomatology and imaging.
 - ⇒ dry cough, shortness of breath, fatigue, and fever
- Disseminated infection causes bilateral adrenal enlargement in 80% of cases and it can result in adrenal insufficiency.
 - Diagnosis: Adrenal biopsy or FNA with Groccott stain (Groccott-stained adrenal biopsy).

Investigation

- Chest X-ray often reveals a solitary lung lesion.
- Disseminated histoplasmosis can cause systemic granulomatous inflammation and cavitation, which may be fatal.
- The organisms can be visualized using methenamine silver or periodic acid-Schiff staining.
- On histology → Macrophages containing yeast
 - ⇒ Histoplasma capsulatum is a small intracellular yeast that is phagocytosed by alveolar macrophages.

Treatment

Itraconazole for 3-6 months

Actinomycosis

Predisposing conditions include:

- tooth extractions.
- fractures of the jaw,
- · periodontal abscesses,
- foreign bodies penetrating the mucosal barrier (bone splinters, fish bones) or
- suppurating tonsillar crypts.
- impaired immunity

Features

- cervicofacial actinomycosis
 - ⇒ the most common manifestation of infection with Actinomyces spp.
- Initially, cervicofacial actinomycosis presents either as an acute, usually odontogenic, abscess or cellulitis of the floor of the mouth, or as a slowly developing hard, painless, reddish or livid swelling.
- Small, acute actinomycotic abscesses may heal after surgical drainage alone. More often, however, the acute initial stage is followed by a subacute to chronic course if no specific antimicrobial treatment is administered.
- Chronic disease is characterised by regression of central suppurative foci while the
 infection progresses peripherally; it can spread to involve other parts of the head and neck,
 including the meninges.
- A quick and comparatively reliable diagnosis is possible microscopically, when sulphur granules are present; this is not conclusive, however, as nocardiosis may present similarly and has a similar appearance on microscopy.
- One way to differentiate Actinomyces spp. from Nocardia spp. is through culture: the former grow in anaerobic conditions and the latter do not.

Malignant otitis externa

Causes

- Malignant otitis externa is a necrotizing infection of the ear that is commonly caused by Pseudomonas aeruginosa.
 - ⇒ Pseudomonas species are often found swimming pools and hot tubs, and can also cause "hot tub folliculitis".

Risk factors

• Susceptible individuals include diabetics and other immunosuppressed patients.

Feature

- Physical exam may reveal discharge from the ear
- severe pain, out of proportion to physical findings, on manipulation of the ear.
- The disease can affect surrounding bony architecture and cause cranial nerve palsies. Such involvement suggests poor prognosis.

Treatment

 Treatment for suspected Pseudomonas infections → anti-pseudomonal penicillin such as piperacillin-tazobactam, which is a penicillin paired with a beta-lactamase inhibitor.

Third edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Dermatology

Updated **2022**

Epidermis

Epidermis - 5 layers - bottom layer = stratum germinativum which gives rise to keratinocytes and contains melanocytes

- The epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina
- It may be divided in to five layers:

Layer	Description	
Stratum corneum	Flat, dead, scale-like cells filled with keratin Continually shed	
Stratum lucidum	Clear layer - present in thick skin only	
Stratum granulosum	Cells form links with neighbours	
Stratum spinosum	Squamous cells begin keratin synthesis Thickest layer of epidermis	
Stratum germinativum	The basement membrane - single layer of columnar epithelial cells Gives rise to keratinocytes Contains melanocytes	

Definitions

- Plaque is a descriptive term for a skin lesion that is raised and greater than 1 cm in diameter.
- Macule is an area of altered skin colour is irrespective of the size.
- Papule is a raised lesion less than 1 cm in diameter.
- Ulcer is a discontinuity of the skin with complete loss of the epidermis and often portions of the dermis and subcutaneous fat.
- **Vesicle** is a fluid-filled, well-circumscribed raised lesion.
- Pustule are small elevation of the skin containing cloudy or purulent material, usually consisting of necrotic inflammatory cells.
- Bulla are large vesicle containing serous fluid.
- Fissure are cracks in the skin that are narrow but deep.
- **Telangiectasia** are collection of enlarged capillaries visible on the skin or mucous membranes.
- Lichenification of the skin is due to epidermal thickening characterised by visible and palpable thickening of the skin with accentuation of skin markings.
- Atrophy of the skin may be due to loss of epidermis, dermis or subcutaneous tissue.
 Thinning of the epidermis presents as skin that appears thin and translucent. Thinning of the dermis and subcutaneous tissue leads to a depression in the skin.

Acanthosis nigricans

Overview

- Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin
- presents as a dark thickened area of the skin of the back of the neck or the armpit,
- Obesity is the most common cause
- Classically acanthosis nigricans associated with malignancy appears abruptly, and it can precede diagnosis of malignancy.
- Diabetes causes acanthosis nigricans due to stimulation of <u>insulin-like growth factor</u> receptor-1.

Causes

- paraneoplastic phenomenon (usually tumours of the GI tract, especially adenocarcinoma of the stomach) and Endometrial carcinoma
- diabetes mellitus
- obesity
- polycystic ovarian syndrome
- acromegaly

- Cushing's disease
- hypothyroidism
- familial (autosomal dominant)
- · Prader-Willi syndrome
- drugs: oral contraceptive pill, nicotinic acid (Niacin)





Management

- first line is treatment of the underlying cause.
- In persistent acanthosis nigricans despite treatment of the underlying cause, topical retinoids can be tried.

Acne rosacea

is a chronic skin disease of unknown aetiology

Features

- · typically affects nose, cheeks and forehead
- flushing is often first symptom
- telangiectasia are common
- later develops into persistent erythema with papules and pustules
- rhinophyma
- · ocular involvement: blepharitis

Management

Acne rosacea treatment:

- · mild/moderate: topical metronidazole
- · severe/resistant: oral tetracycline
- topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques)
- · more severe disease is treated with systemic antibiotics e.g. Oxytetracycline
- recommend daily application of a high-factor sunscreen
- camouflage creams may help conceal redness
- laser therapy may be appropriate for patients with prominent telangiectasia

Acne vulgaris

- Acne vulgaris is a common skin disorder which usually occurs in adolescence.
- It typically affects the face, neck and upper trunk
- characterised by the obstruction of the pilosebaceous follicle with keratin plugs which results in comedones, inflammation and pustules.

Epidemiology

- Affects around 80-90% of teenagers
- **Age of onset:** typically by 11–12 years, with symptoms usually disappearing around 20–30 years of age
 - ⇒ Acne presenting at beyond aged 20 years should always prompt investigation of a possible secondary cause.
- Sex: more common in males during adolescence, but more common in women during adulthood

Aetiology & Pathophysiology

- Hormonal factors
 - $\Rightarrow \uparrow$ Androgens during puberty \rightarrow increased production of sebum by sebaceous glands
 - ⇒ In women: menstrual cycle
- **Follicular hyperkeratosis**: Follicular epidermal hyperproliferation → formation of a keratin plug → obstruction of pilosebaceous follicle. Higher keratinocyte activity and decreased keratinocyte shedding in pilosebaceous units leads to the formation of comedones.
- **Bacterial colonisation** with Cutibacterium acnes; inflammatory reactions with formation of papules, nodules, pustules, and/or cysts

Features

- Localisation: common in areas with sebaceous glands (predilection sites: face, shoulders, upper chest, and back)
- Primary lesions

- ⇒ Non-inflammatory: comedonal acne
 - Closed comedones ("whiteheads"): closed small round lesions that contain whitish material
 - Open comedones ("blackheads"): dark, open portion of sebaceous material
- ⇒ Inflammatory: affected areas are red and can be painful
 - papules, pustules that arise from comedones
 - Nodular acne (> 5 mm in diameter): Commonly the back and neck
- Secondary lesions: hyperpigmentation, and scarring

Management

- A simple step-up management scheme often used in the treatment of acne is as follows:
 - ⇒ Single topical therapy (topical retinoids, benzyl peroxide)
 - ⇒ Topical combination therapy (topical antibiotic, benzoyl peroxide, topical retinoid)
 - ⇒ Oral antibiotics: e.g. Oxytetracycline, doxycycline.
 - Improvement may not be seen for 3-4 months.
 - Minocycline is now considered less appropriate due to the possibility of irreversible pigmentation.
 - Gram negative folliculitis may occur as a complication of long-term antibiotic use . high-dose oral trimethoprim is effective if this occurs
 - Oral erythromycin may be used for acne in pregnancy. The other drugs are contraindicated
- Oral isotretinoin: only under specialist supervision
- Ethinylestradiol with cyproterone acetate (Dianette) is useful in some female patients with acne unresponsive to standard treatment.
- . There is no role for dietary modification in patients with acne

Weight loss is the most important intervention.

Isotretinoin

Retinoid (isotretinoin) therapy should be discontinued at the latest one month before

Overview

 Isotretinoin is an oral retinoid used in the treatment of severe acne. Two-thirds of patients have a long-term remission or cure following a course of oral isotretinoin

Indication

Moderate to severe acne

Contraindications

- Pregnancy, women of childbearing age without contraception: strong teratogenic effects
- Liver disease
- Precautions (in all females of childbearing potential)
- A serum/urine pregnancy test

Side effects

- Teratogenicity
 - ⇒ females should ideally be using two forms of contraception (e.g. Combined oral contraceptive pill and condoms)
 - ⇒ should be discontinued at the latest one month before
- Dry skin, eyes and lips: the most common side-effect of isotretinoin
- Low mood
- Raised triglycerides
- Hair thinning

- Nose bleeds (caused by dryness of the nasal mucosa)
- Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason
- Photosensitivity
- Laboratory test abnormalities: ↑ Triglycerides, ↓ HDL, ↑ glucose

Alopecia

Divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle)

Scarring alopecia

- trauma, burns
- radiotherapy
- lichen planus
- discoid lupus
- tinea capitis (scarring may develop in untreated tinea capitis if a kerion develops)

Non-scarring alopecia

- male-pattern baldness
- drugs: cytotoxic drugs, carbimazole, heparin, oral contraceptive pill, colchicine
- · nutritional: iron and zinc deficiency
- · autoimmune: alopecia areata
- telogen effluvium (hair loss following stressful period e.g. surgery)
- trichotillomania
 - psychological disorder where patients are compelled to pull their own hair, resulting in alopecia.
 - ⇒ It is typically encountered in teenage females and children

Cicatricial alopecia (also known as scarring alopecia)

- inflammation injures hair follicles resulting in permanent bald patches with no visible follicles.
 - ⇒ inflammation can be seen as redness, scaling and crusting.
- · Common causes include:
 - ⇒ discoid lupus ervthematosus, and
 - ⇒ lichen planopilaris (a variant of lichen planus).
- Treatment is dependent on the underlying causes but often requires topical corticosteroids.

Alopecia areata

 Alopecia areata is a presumed autoimmune condition causing localised, well demarcated patches of hair loss.

Feature

- localised patches of non-scarring hair loss.
- Remaining hairs have a characteristic 'exclamation mark' appearance, and are tapered towards the base.
 - ⇒ small, broken hairs at the edge of the hair loss
- More severe involvement may present as alopecia totalis (total loss of scalp hair) or alopecia universalis (total loss of all body hair).

Treatment

- Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually. Careful explanation is therefore sufficient in many patients.
- Other treatment options include:

- ⇒ topical or intralesional corticosteroids
 - the most appropriate treatment for area of hair loss → Intra-lesional triamcinolone
- ⇒ topical minoxidil
- ⇒ phototherapy
- ⇒ contact immunotherapy
- ⇒ wigs

Differential diagnosis

- Androgenetic alopecia
 - ⇒ presents after puberty as a more diffuse slow hair loss with characteristic loss over the temporal regions and vertex in males.
- Discoid lupus erythematosus (DLE)
 - ⇒ presents as scarring alopecia.
 - ⇒ Areas of alopecia are usually atrophic with visible loss of hair follicles.
 - ⇒ Patients may have DLE lesions elsewhere.
 - ⇒ If not treated early, hair loss is usually irreversible.

• Telogen effluvium

- ⇒ presents with diffuse hair loss and usually presents one to three months after a stressful episode, for example, viral illness, surgery, childbirth, emotional stress.
- ⇒ Hair loss is never complete and usually stops after three to five months.
- ⇒ Subsequent hair regrowth is usually complete.

Trichotillomania

- ⇒ more commonly seen in children compared to adults.
- ⇒ Patients also present with localised hair loss but in a bizarre pattern.
- ⇒ Hairs of differing lengths are usually seen within and at the edges of the patches.
- ⇒ Patients may or may not volunteer a history of hair pulling.

Pemphigus vulgaris

Blisters/bullae

- · no mucosal involvement: bullous pemphigoid
- mucosal involvement: pemphigus vulgaris

Overview

- Pemphigus vulgaris is an autoimmune disease caused by antibodies (IgG) directed against desmoglein 3, a cadherin-type epithelial cell adhesion molecule.
- The binding of autoantibodies results in a loss of cell-to-cell adhesion, a process termed acantholysis.
- It is more common in the Ashkenazi Jewish population
- seen predominantly in patients ages 50-60, but can affect many ages.

Features

- mucosal ulceration is common and often the presenting symptom. Oral involvement is seen in 50-70% of patients
- skin blistering flaccid, easily ruptured vesicles and bullae.
 - ⇒ Blisters are thin-walled and rupture easily (intact blisters are rarely seen).
- Lesions are typically painful but not itchy. These may develop months after the initial mucosal symptoms.
- Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin

Immunofluorescent staining of a biopsy sample shows deposition of immunoglobulin (IgG)
directed against to keratinocyte desmosomes and to desmosome-free areas of the
keratinocyte cell membrane, resulting in a 'chicken wire' appearance.

acantholysis on biopsy





Mucosal ulceration is common with pemphigus

Management

- steroids
- · immunosuppressants

Bullous pemphigoid

Overview

- Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin.
- This is secondary to the development of antibodies against hemidesmosomal proteins BP180 and BP230
 - ⇒ caused by (IgG) autoantibodies against components of the basement membrane.

Epidemiology

- Pemphigoid, erythema multiforme, and herpes are the commonest causes of a blistering rash.
- Bullous pemphigoid is more common in elderly patients (over 60 years).
 - ⇒ Remember, this is a disease of the elderly (uncommon under the age of 60).

Features

- Include
- itchy, tense blisters typically around flexures
- the blisters usually heal without scarring
- mouth is usually spared*
 - ⇒ *in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.

Investigations

- Skin biopsy:
 - **⇒** Perilesional skin biopsy for examination by direct immunofluorescence
 - ⇒ immunofluorescence shows IgG and C3 at the dermo-epidermal junction

Differential diagnosis

 Blistering in pemphigoid occurs at the sub-epidermal level - deeper than the blisters of pemphigus vulgaris (which occur at the dermal-epidermal junction); hence the tense blisters seen in pemphigoid. Blisters are thin-walled and fragile in pemphigus - few intact blisters are ever seen. ⇒ In pemphigus vulgaris, mucous membrane involvement is more common, and intact bullae are rare. Skin biopsy for routine and direct immunofluorescence is needed to differentiate from bullous pemphigoid.

Management

- referral to dermatologist for biopsy and confirmation of diagnosis
- oral corticosteroids are the mainstay of treatment
- topical corticosteroids, immunosuppressants and antibiotics are also used

⇒ Topical corticosteroids may be attempted in patients with mild, localised bullous pemphigoid.





	Pemphigus vulgaris	Bullous pemphigoid
Appearance		
Age	Younger	Older
Mucous membrane involvement	Yes	Rare
Autoantibodies	Against desmoglein 3	Against hemidesmosomes
Blister location	Intraepidermal (superficial)	Subepidermal (deep)
Blister quality	Flaccid, rupture easily	Tense and firm
Nikolsky's sign	Nikolsky positive	Nikolsky negative
Prognosis	Poor	Favorable

Dermatitis herpetiformis (DH)

Dermatitis herpetiformis is associated with HLA-DR3

Dermatitis herpetiformis - caused by IgA deposition in the dermis

Overview

- autoimmune blistering skin disorder associated with coeliac disease and gluten sensitivity.
- caused by deposition of IgA in the dermis.
- · associated with HLA-DR3.
- Virtually all patients with DH carry the HLA DQ2 or HLA DQ8 haplotype.

Features

itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

Association

- increased risk for the development of other autoimmune diseases.
 - ⇒ Thyroid disease is the most common autoimmune disorder associated with DH.
- · increased risk for lymphoma.

Diagnosis

- skin biopsy: direct immunofluorescence (The gold standard test for diagnosis) shows:
 - ⇒ Subepidermal deposition of IgA
 - in a granular pattern in the upper dermis (in the dermal papillae)(Granular IgA deposits at the basement membrane zone)
 - ⇒ neutrophilic dermal infiltrates in the superficial dermis
 - Neutrophils are the immune cell that is involved in the blistering skin lesion DH.
- Serology
 - ⇒ blood test showing the presence of IgA antibodies against tissue transglutaminase.

Management

- gluten-free diet
- dapsone





Dermatitis herpetiformis

Discoid lupus erythematous

Pathology

- it is a chronic type of Cutaneous lupus erythematosus (CLE)
- · characterised by follicular keratin plugs
- characterised by a well-demarcated macular rash with erythema, scales, and plaques that often results in scarring and atrophy.

Aetiology

• thought to be autoimmune in aetiology

Association

- may occur in the absence or in association with systemic SLE.
 - ⇒ Approximately 10% of patients may have signs of SLE.

Epidemiology

- · generally seen in younger females.
- occurs 2-3 times more frequently in women than in men
- more common in African–Caribbean female.

Features

- erythematous, raised rash, sometimes scaly
- · may be photosensitive
- · more common on face, neck, ears and scalp
- lesions heal with atrophy, scarring (may cause scarring alopecia), and pigmentation

Diagnosis

· made by biopsy of the lesion.

Management

Discoid lupus erythematous - topical steroids \rightarrow oral hydroxychloroquine

- 1st line: topical potent steroid cream
- 2nd line: oral antimalarials e.g. hydroxychloroquine
 - ⇒ other options
 - Topical calcineurin inhibitors
 - Intralesional corticosteroids
 - Oral corticosteroids.
- Avoid sun exposure

Prognosis

- The risk of progression to SLE in patients with DLE was demonstrated to be higher than previously reported (16.7% progression within 3 years of diagnosis, as compared with previous data indicating that <5-10% of patients with DLE progress to SLE).
- **children** with DLE seem to have a higher early rate of progression to SLE (up to **25%**) indicating that the **age at onset might influence disease severity**

According to a recent epidemiologic study, approximately 16% of patients with discoid lupus erythematosus (DLE) may develop systemic involvement within 3 years of diagnosis.



Contact dermatitis

Types

- There are two main types of contact dermatitis
 - ⇒ Irritant contact dermatitis:
 - common
 - non-allergic reaction due to weak acids or alkalis (e.g. detergents).
 - Often seen on the hands.
 - Erythema is typical, crusting and vesicles are rare
 - ⇒ Allergic contact dermatitis:
 - type IV hypersensitivity reaction.
 - Uncommon
 - often seen on the head following hair dyes.
 - Presents as an acute weeping eczema, which predominately affects the margins of the hairline rather than the hairy scalp itself.
 - Topical treatment with a potent steroid is indicated

The main difference between allergic contact dermatitis and irritant contact dermatitis:

- ⇒ The rash caused by allergic contact dermatitis confined to contacted area, whereas in irritant contact dermatitis, the rash is more widespread.
- □ In allergic contact dermatitis the rash usually appears after a day or two after exposure to the allergen, unlike irritant contact dermatitis that appears immediately after the contact with the trigger.

Pruritus

Causes

The table below lists the main characteristics of the most important causes of pruritus

Liver disease	History of alcohol excess Stigmata of chronic liver disease: spider naevi, bruising, palmar erythema, gynaecomastia etc Evidence of decompensation: ascites, jaundice, encephalopathy
Iron deficiency	Pallor
anaemia	Other signs: koilonychia, atrophic glossitis, post-cricoid webs, angular stomatitis
Polycythaemia	Pruritus particularly after warm bath 'Ruddy complexion' Gout Peptic ulcer disease
Chronic kidney disease	Lethargy & pallor Oedema & weight gain Hypertension
Lymphoma	Night sweats Lymphadenopathy Splenomegaly, hepatomegaly Fatigue
Other causes	 hyper- and hypothyroidism diabetes pregnancy 'senile' pruritus skin disorders: eczema, scabies, psoriasis, pityriasis rosea Idiopathic urticaria: Up to 50% of cases are idiopathic

Eczema herpeticum

• Eczema herpeticum describes a severe primary infection of the skin by herpes simplex virus 1 or 2.

Features

- It is more commonly seen in children with atopic eczema.
- Typically, the child has a high fever for seven days, and recurrent attacks can occur.
- It may affect any site but is most often seen on face and neck.

Treatment

- Eczema herpeticum is considered as one of the few dermatological emergencies.
- As it is potentially life threatening children should be admitted for IV acyclovir

Complications

- Death can result from physiological disturbances (loss of fluid electrolytes and protein through the skin) or dissemination of the virus to brain and other organs or from secondary bacterial sepsis.
- may be further complicated by secondary staphylococcal infection. This is treated by adding oral antibiotics, for example, flucloxacillin 500 mg q.i.d.

Eczema: topical steroids

Topical steroids

moderate: Clobetasone butyrate 0.05%

potent: Betamethasone valerate 0.1%

very potent: Clobetasol propionate 0.05%

Use weakest steroid cream which controls patients symptoms

The table below shows topical steroids by potency

Mild	Moderate	Potent	Very potent
Hydrocortisone 0.5-2.5%	Betamethasone valerate 0.025% (Betnovate RD)	Fluticasone propionate 0.05% (Cutivate)	Clobeta sol propionate 0.05% (Dermovate)
	Clobeta sone butyrate 0.05% (Eumovate)	Betamethasone valerate 0.1% (Betnovate)	

Finger tip rule

 1 finger tip unit (FTU) = 0.5 g, sufficient to treat a skin area about twice that of the flat of an adult hand

Topical steroid doses for eczema in adults

Area of skin	Fingertip units per dose
Hand and fingers (front and back)	1.0
A foot (all over)	2.0
Front of chest and abdomen	7.0
Back and buttocks	7.0
Face and neck	2.5
An entire arm and hand	4.0
An entire leg and foot	8.0

The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

Area	Amount
Face and neck	15 to 30 g
Both hands	15 to 30 g
Scalp	15 to 30 g
Both arms	30 to 60 g
Both legs	100 g
Trunk	100 g
Groin and genitalia	15 to 30 g

Pompholyx

Pompholyx is a type of eczema which affects both the hands (cheiropompholyx) and the feet (pedopompholyx). It is also known as dyshidrotic eczema

Features

- small blisters on the palms and soles
- · pruritic, sometimes burning sensation
- once blisters burst skin may become dry and crack

Management

- · cool compresses
- emollients
- topical steroids

Erythema ab igne

- Erythema ab igne is a skin disorder caused by over exposure to infrared radiation.
- It classically presents on the front of the legs due to the patient sitting too close to a fire or heater. It may also arise as a response to chronic hot water bottle use.
- Characteristic features include reticulated, erythematous patches with hyperpigmentation and telangiectasia.
- A typical history would be an elderly women who always sits next to an open fire.
- Hypothyroidism can make patients feel cold and hence more likely to sit next a heater / fire.
- If the cause is not treated then patients may go on to develop squamous cell skin cancer.





Erythema ab igne Erythema ab igne

Erythema multiforme

Pathophysiology

- Type IV hypersensitivity reaction; triggered by the following
 - ⇒ Infections: herpes simplex virus (HSV the most common cause), Mycoplasma pneumoniae.
 - ⇒ Drugs: phenytoin; beta-lactam antibiotics (e.g., penicillins); sulfonamides

Classification

- Erythema multiforme minor (typical targets or raised oedematous papules, with acral distribution, without involvement of mucosal sites, and involving <10% total body surface
- Erythema multiforme major (typical targets or raised oedematous papules, with acral distribution, plus involvement of 1 or more mucosal sites, and involving <10% total body surface area)

Features

- Erythematous, maculopapular rash (many forms), hence the 'multiforme' in the name.
- Target lesions (also called iris lesion): an inner dark red/brown zone, surrounded by a pale zone, and an outer erythematous ring.
- Distribution: Symmetrical and affects backs of hands and feet first → spreads proximally and can affect the entire body.

Treatment

Supportive: treat the underlying infection or stop the offending drug.

Prognosis

 usually mild and self-limiting disease with the lesions healing within 2 to 3 weeks without scarring.



Erythema multiforme



Erythema multiforme

Differential diagnosis

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the same entity but differ in terms of disease severity (based on surface area of skin involved).
 - ⇒ < 10% SJS
 - ⇒ 10–30% SJS/TEN overlap
 - ⇒ 30% Toxic epidermal necrolysis (severe SJS)

Erythema multiforme VS Stevens-Johnson syndrome

	Erythema multiforme (EM)	Stevens-Johnson syndrome (SJS)
Causes	usually triggered by infections, most commonly herpes simplex virus (HSV). Medications are uncommon cause (<10%)	Most commonly triggered by drugs (\sim 80%).
Lesions distribution	Lesions begin on the extremities	Lesions typically begin on the face and trunk.
Target lesions	Typical target lesions	No typical target lesions.
Mucosal membranes	Mucosal membranes may be involved, but usually not	Mucosal membranes almost always involved
Swelling	No associated swelling of face, hands or feet	Associated swelling of face, hands or feet
Systemic symptoms	Systemic symptoms such as fever and malaise, are absent or mild	Systemic symptoms such as fever and malaise, are prominent
Histology	high density of cell infiltrate rich in T- lymphocytes. (more dermal inflammation and individual keratinocyte necrosis)	poor infiltrate of macrophages and dendrocytes with tumor necrosis factor (TNF) (minimal inflammation and sheets of epidermal necrosis.)
Severity	Usually mild	Shock may develop
Treatment	Treat underline cause	need urgent supportive care , fluid resuscitation similar to that of burns and Wound management
Prognosis	Self-limiting	High mortality rate (SJS: ~ 25%, TEN: ~ 50%)

Erythema multiforme (EM):

- a type IV hypersensitivity reaction of the skin.
- can be triggered by certain infections (e.g., HSV, Mycoplasma pneumonia) and medications (e.g., beta-lactam antibiotics, sulfonamides, phenytoin).

Erythema multiforme (EM):

 EM is characterized by lesions of varying morphology (e.g., macules, papules, vesicles) that typically progress to <u>target lesions</u> and spread proximally from the backs of the hands and feet.

Herpes simplex virus (HSV) infection is the commonest cause of Erythema multiforme

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Definition

- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe
 mucocutaneous reactions, most commonly triggered by medications, characterized by
 extensive necrosis and detachment of the epidermis
- SJS and TEN are the same entity but differ in terms of disease severity (based on surface area of skin involved).

 - ⇒ 10–30% SJS/TEN overlap
 - ⇒ ≥ 30% Toxic epidermal necrolysis (severe SJS)

Pathophysiology

Delayed hypersensitivity reaction (type IV)

Causes

- Most commonly triggered by medications, \sim 80% of cases
 - ⇒ Antibiotics: sulfonamides (e.g., TMP/SMX), aminopenicillins
 - Antiepileptics: phenytoin, phenobarbital, lamotrigine, valproic acid, carbamazepine,
 - ⇒ Sulfasalazine
 - ⇒ Nonsteroidal anti-inflammatory drugs (NSAIDs)

Features

- Begins with a prodrome of fever and influenza-like symptoms one to three days before the development of mucocutaneous and skin lesions.
- Extensive, full-thickness epidermal necrosis and sloughing (resembling large superficial burns)
- Mucosal membranes: almost always involved ~ 90% of cases
- Systemically unwell e.g. pyrexia, tachycardic, shock may develop
- Positive Nikolsky's sign (the epidermis separates with mild lateral pressure)
- Skin biopsy
 - ⇒ Keratinocyte necrosis with apparent subepidermal split
 - ⇒ Eosinophilic infiltration with minimal infiltration of lymphocytes and histiocytes around blood vessels

Treatment

- Stop precipitating factor is most likely to improve prognosis
- Supportive care, often in intensive care unit
- Wound management: similar to that of burns



Stevens-Johnson syndrome (SJS)

Erythema nodosum

Always do a chest x-ray on a patient with erythema nodosum, to exclude sarcoidosis

Overview

- inflammation of subcutaneous fat
- Histology of these lesions shows a vasculitis of small venules and panniculitis.
- typically causes tender, erythematous, nodular lesions
- usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs)
- · usually resolves within 6 weeks
- lesions heal without scarring

Causes

- infection: streptococci, TB, brucellosis
 - ⇒ The commonest cause is streptococcal infection.
- systemic disease: sarcoidosis, inflammatory bowel disease (ulcerative colitis), Behcet's, SLE
- · malignancy/lymphoma
- Drugs (oral contraceptive, sulfonamides, penicillins, antipyretics, montelukast, Hep B vaccination, omeprazole).







Erythema induratum (EI)

- El is a form of panniculitis characterised by chronic, recurrent, tender, subcutaneous, and sometimes <u>ulcerated</u> nodules on the lower legs that may also appear elsewhere.
 - ⇒ (Erythema nodosum also commonly associated with TB but do not ulcerate)
- Females are more frequently affected, with a female: male ratio of 7:1 and it is more frequent in younger females.
- It is found in association with tuberculosis.

Erythrasma

- Erythrasma is a generally asymptomatic, flat, slightly scaly, pink or brown rash usually found in the groin or axillae.
- It is caused by an overgrowth of the diphtheroid Corynebacterium minutissimum
- Examination with Wood's light reveals a coral-red fluorescence.
- Topical miconazole or antibacterial are usually effective. Oral erythromycin may be used for more extensive infection

Erythroderma

- Erythroderma is a term used when more than 95% of the skin is involved in a rash of any kind
- Mechanism
 - ⇒ The mechanism behind erythroderma is most likely from cutaneous thermal dysregulation.
 - Increased blood flow to the skin leads to heat and fluid loss, and increased rate of skin cell turnover and skin sloughing.
- · Causes of erythroderma
 - ⇒ Eczema (40%)
 - ⇒ Psoriasis (25%)
 - ⇒ drugs e.g. gold
 - ⇒ lymphoma, leukaemia
 - ⇒ pityriasis rubra pilaris
- often accompanied with fever, shivering and malaise.
- Erythrodermic psoriasis
 - ⇒ may result from progression of chronic disease to an exfoliative phase with plaques covering most of the body. Associated with mild systemic upset
 - ⇒ more serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management



This image shows the generalised erythematous rash seen in patients with erythroderma, sometimes referred to as 'red man syndrome'



Note the extensive exfoliation seen in this patient

Fungal nail infections

Onychomycosis is fungal infection of the nails. This may be caused by

- dermatophytes mainly Trichophyton rubrum, accounts for 90% of cases
- · yeasts such as Candida
- non-dermatophyte moulds

Features

- 'unsightly' nails are a common reason for presentation
- · thickened, rough, opaque nails are the most common finding

Investigation

- · nail clippings
- · scrapings of the affected nail
- Wood's lamp
 - ⇒ useful, rapid and easy way to confirm the diagnosis
 - Yellow to yellow-green fluorescence is characteristic of fine scales taken from active fungal lesions
 - ⇒ the sensitivity of this procedure is reduced when patients have taken a recent shower

Management

Dermatophyte nail infections - use oral terbinafine

- treatment is successful in around 50-80% of people
- diagnosis should be confirmed by microbiology before starting treatment
- dermatophyte infection:
 - ⇒ first-line: oral terbinafine
 - ⇒ alternative: oral itraconazole.
 - ⇒ Treatment duration:
 - for fingernail infections → 6 weeks 3 months
 - for toenails → 3 6 months
- Candida infection: mild disease should be treated with topical antifungals (e.g. Amorolfine)
 whilst more severe infections should be treated with oral itraconazole for a period of 12
 weeks

Beau's lines

Beau's lines is a benign nail condition that presents as a jagged transverse groove on the
nail plate corresponding to an episode of nail growth arrest, which can occur during an
episode of severe medical illness. It usually affects several nails.



Beau's lines

Nail conditions

- **Fungal nail infections** present with thickening and discolouration of the nail plate with prominent subungual debris. It usually only affects one or several nails.
- Nail psoriasis presents with pitting, onycholysis, subungual debris and yellowish nail discolouration.

Granuloma annulare

Basics

- Granuloma annulare is a benign inflammatory condition of unknown aetiology
- characterised by dermal papules which can coalesce to form annular plagues.
- · papular lesions that are often slightly hyperpigmented and depressed centrally
- typically occur on the dorsal surfaces of the hands and feet, and on the extensor aspects of the arms and legs
- Histology reveals foci of degenerative collagen surrounded by areas of granulomatous inflammation.
- A number of associations have been proposed to conditions such as diabetes mellitus but there is only weak evidence for this
- Treatment → Observation (The eruption should disappear spontaneously.)
- Locally delivered steroids are effective in resolving the condition.





Granuloma annulare

Herpes simplex virus

Overview

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

Features

- primary infection: may present with a severe gingivostomatitis
- · cold sores
- painful genital ulceration

Management

- · gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest
- · genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Pregnancy

 elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation

Molluscum contagiosum

Definition: A common skin infection caused by molluscum contagiosum virus (MCV), DNA poxvirus

Transmission: Direct skin contact (contact sports, sexually transmitted), autoinoculation or indirectly via fomites (contaminated surfaces) such as shared towels and flannels.

Risk factors:

- Most common in children (often in children with atopic eczema)
- Immunosuppression → HIV testing if lesions in adults and/or widespread

Presentation

 dome-shaped, smooth, pinkish or pearly white papules with a central umbilication, which are up to 5 mm in diameter. commonly seen on the trunk and in flexures.

Treatment

- Usually self-limiting condition → Watchful waiting (especially in children)
- Self-care advice: avoid direct contact and sharing towels. Exclusion from school, gym, or swimming is not necessary.
- For cosmetic or lesions in the genital area:
 - ⇒ Cryotherapy is the first-line treatment
 - ⇒ Topical cantharidin



Molluscum contagiosum

Impetigo

Impetigo - topical fusidic acid ightarrow oral flucloxacillin / topical retapamulin

Impetigo is a superficial bacterial skin infection usually caused by either *Staphylcoccus* aureus or *Streptococcus* pyogenes.

Features

- 'golden', crusted skin lesions typically found around the mouth
- very contagious

Management

- · Limited, localised disease
 - ⇒ topical fusidic acid is first-line
 - topical retapamulin is used second-line if fusidic acid has been ineffective or is not tolerated
 - ⇒ MRSA is not susceptible to either fusidic acid or retapamulin. Topical mupirocin (Bactroban) should therefore be used in this situation
- · Extensive disease
 - ⇒ oral flucloxacillin
 - ⇒ oral erythromycin if penicillin allergic





Erysipelas

• Erysipelas is a *Streptococcus pyogenes* (a group A streptococcal bacterium) infection of the deep dermis and subcutis.

Feature

- It is a tender, intensely erythematous, indurated plaque with a sharply demarcated border.
- Its well-defined margin can help differentiate it from other skin infections (eg, cellulitis).

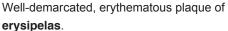
Treatment

- IV antibiotics such as benzylpenicillin and erythromycin.
- In a penicillin allergic patient a macrolide is the drug of choice .There is a 10% cross allergy between cephalosporins and penicillins.

Complications

- sepsis
- · cerebral abscess
- · venous sinus thrombosis.







Koebner phenomenon

Describes skin lesions which appear at the site of injury. It is seen in:

- psoriasis
- vitiligo
- warts
- lichen planus
- lichen sclerosus
- molluscum contagiosum

Lichen planus

Lichen

- planus: purple, pruritic, papular, polygonal rash on flexor surfaces. Wickham's striae over surface. Oral involvement common
- sclerosus: itchy white spots typically seen on the vulva of elderly women

Lichen planus is a skin disorder of unknown aetiology, most probably being immune mediated.

Features

- · itchy, papular rash most common on the palms, soles, genitalia and flexor surfaces of arms
- rash often polygonal in shape, 'white-lace' pattern on the surface (Wickham's striae)
- Koebner phenomenon may be seen (new skin lesions appearing at the site of trauma)
- oral involvement in around 50% of patients
- nails: thinning of nail plate, longitudinal ridging
- Fibrin deposits at the basement membrane zone are found in cases of lichen planus, although immunofluorescence studies are uncommonly done to diagnose it.







Lichenoid drug eruptions - causes:

- gold
- quinine
- thiazides

Management

- · topical steroids are the mainstay of treatment
- extensive lichen planus may require oral steroids or immunosuppression

Lichen sclerosus

- Lichen sclerosus was previously termed lichen sclerosus et atrophicus.
- It is an inflammatory condition which usually affects the genitalia and is more common in elderly females.
- · Lichen sclerosus leads to atrophy of the epidermis with white plaques forming

Features

itch is prominent

Diagnosis

 usually made on clinical grounds but a biopsy may be performed if atypical features are present*

Management

· topical steroids and emollients

Follow-up

· increased risk of vulval cancer

*the RCOG advise the following

Skin biopsy is not necessary when a diagnosis can be made on clinical examination. Biopsy
is required if the woman fails to respond to treatment or there is clinical suspicion of VIN or
cancer.

and the British Association of Dermatologists state the following:

- A confirmatory biopsy, although ideal, is not always practical, particularly in children. It is
 not always essential when the clinical features are typical. However, histological
 examination is advisable if there are atypical features or diagnostic uncertainty and is
 mandatory if there is any suspicion of neoplastic
 change.
- Patients under routine follow-up will need a biopsy if:
 - (i) there is a suspicion of neoplastic change, i.e. a persistent area of hyperkeratosis, erosion or erythema, or new warty or papular lesions;
 - (ii) the disease fails to respond to adequate treatment;
 - (iii) there is extragenital LS, with features suggesting an overlap with morphoea;
 - (iv) there are pigmented areas, in order to exclude an abnormal melanocytic proliferation:
 - (v) second-line therapy is to be used.

Lichen simplex chronicus (LSC)

- LSC presents with hyperpigmented, scaly, lichenified plaques.
- Patients may volunteer a history of chronic scratching or manipulation, especially during times of stress.
- The ankles are common sites for LSC.



Lichen amyloidosis

- Lichen amyloidosis is a primary, localised cutaneous amyloidosis (amyloid deposition in the skin).
- It results in intensely itchy shiny or hyperkeratotic, pigmented macules and occurs most commonly in South East Asia.
- It appears that itching drives further amyloid deposition, and treatments are therefore
 directed at reducing the sensation of itching for example, with the use of antihistamines
 and intra-lesional/topical corticosteroids.



Lichen amyloidosis

Onvcholysis

Onycholysis describes the separation of the nail plate from the nail bed

Causes

- idiopathic
- · trauma e.g. Excessive manicuring
- infection: especially fungal
- · skin disease: psoriasis, eczema, dermatitis
- impaired peripheral circulation e.g. Raynaud's
- systemic disease: hyper- and hypothyroidism
- Tetracycline

Parvovirus B19

Parvovirus B19 is a DNA virus which causes a variety of clinical presentations. It was identified in the 1980's as the cause of erythema infectiosum

Erythema infectiosum (also known as fifth disease or 'slapped-cheek syndrome')

- · most common presenting illness
- systemic symptoms: lethargy, fever, headache
- 'slapped-cheek' rash spreading to proximal arms and extensor surfaces

Other presentations

- asymptomatic
- pancytopaenia in immunosuppressed patients
- aplastic crises e.g. in sickle-cell disease (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anaemia is rare unless there is a chronic haemolytic anaemia)

Pityriasis rosea

- describes an acute, self-limiting rash which tends to affect young adults. occurs most commonly in people between the ages of 10 and 35 years.
- The aetiology is not fully understood but is thought that herpes hominis virus 7 (HHV-7) may play a role. does not appear to be contagious;
- · aetiology is unknown

Features

- herald patch (usually on trunk)
- followed by erythematous, oval, scaly patches which follow a characteristic distribution
 with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This
 may produce a 'fir-tree' appearance
- · can be pruritic or asymptomatic

Management

- self-limiting, usually disappears after 4-12 weeks
- moisturisers can help the pruritus



On the left a typical herald patch is seen. After a few days a more generalised 'fir-tree' rash appears

Pityriasis versicolor

also called tinea versicolor, is a superficial cutaneous fungal infection caused by Malassezia furfur (formerly termed Pityrosporum ovale)

Features

- most commonly affects trunk
- patches may be hypopigmented, pink or brown (hence versicolor)
- · scale is common
- mild pruritus

Predisposing factors

- occurs in healthy individuals
- immunosuppression
- malnutrition
- Cushing's

Management

- topical antifungal. NICE Clinical Knowledge Summaries advise ketoconazole shampoo as this is more cost effective for large areas
- Topical selenium sulphide
- if extensive disease or failure to respond to topical treatment then consider oral itraconazole 200 mg once a day for seven days.

Psoriasis

Definition

 Psoriasis is a chronic relapsing inflammatory skin disorder most commonly characterised by erythematous, sharply demarcated papules and rounded plaques covered by silvery scales.

Epidemiology

- prevalence around 2%.
- there are two peaks of incidence at 16-22 years and 57-60 years.
- Males and females are equally affected.

Pathophysiology

- · multifactorial and not yet fully understood
 - ⇒ genetic:
 - polygenic inheritance

- associated HLA-B13, -B17, and -Cw6.
- European populations are commonly affected,
- Strong concordance (70%) in identical twins
- ⇒ immunological:
 - abnormal T cell activity stimulates keratinocyte proliferation.
 - may be mediated by T helper cells producing IL-17.
 - IL-17 is a pro-inflammatory cytokine which is expressed at high levels in psoriasis lesions.
 - Ixekizumab is an anti-IL-17 antibody which binds to IL-17, it is effective in treating active psoriasis and in reducing the risk of recurrence.
- ⇒ environmental:
 - psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors
- increase in mitotic activity of the cells in the malpighian layer of the epidermis
 - ⇒ The Malpighian layer of the skin is generally defined as both the stratum basalis and stratum spinosum as a unit.

Recognised subtypes of psoriasis

- plaque psoriasis: the most common sub-type resulting in the typical well demarcated red, scaly patches affecting the extensor surfaces, sacrum and scalp
- **flexural psoriasis**: in contrast to plaque psoriasis the skin is smooth
- guttate psoriasis: transient psoriatic rash frequently triggered by a streptococcal infection.
 Multiple red, teardrop lesions appear on the body
- pustular psoriasis: commonly occurs on the palms and soles





Features

- Salmon colored skin plaques with silvery scales
- Psoriasis may occur in hidden sites, such as the scalp (where psoriasis frequently is mistaken for dandruff), perineum, intergluteal cleft, and umbilicus
 - The scalp is often involved in psoriasis. Most commonly, it causes a telogen effluvium, that is, the hair follicles are forced into the telogen resting stage.

Other features

- · nail signs: pitting, onycholysis
- arthritis
- New lesions often appear at sites of injury or trauma (Koebner phenomenon), which
 typically occurs one to two weeks after the skin has been damaged.
- Auspitz sign: small bleeding spots when psoriasis scales are scraped off.
- Psoriasis can be associated with an anterior uveitis

Complications

- psoriatic arthropathy (around 10%)
 - ⇒ This can range from mild distal interphalangeal joint involvement with nail pitting to severe arthritis mutilans.

- increased incidence of metabolic syndrome
- increased incidence of cardiovascular disease
- increased incidence of venous thromboembolism
- psychological distress

Diagnosis

- usually clinical
- skin biopsy is rarely required to confirm psoriasis.
 - ⇒ Hyperkeratosis (described as an increased thickness of the stratum corneum),
 - ⇒ <u>Parakeratosis</u>, defined as hyperkeratosis with <u>retention</u> of nuclei in the stratum corneum.
 - Munro's microabscess (or neutrophils) in the <u>stratum corneum</u> of the epidermis are a cardinal sign

Exacerbating factors

Psoriasis: common triggers are beta-blockers and lithium

- trauma
- alcohol
- drugs:
 - ⇒ beta blockers.
 - ⇒ lithium.
 - ⇒ antimalarials (chloroguine and hydroxychloroguine),
 - ⇒ gold salts,
 - ⇒ NSAIDs,
 - ⇒ ACE inhibitors,

 - ⇒ antibiotics such as tetracycline and penicillin
- withdrawal of systemic steroids
- Notes
 - ⇒ Reactions may occur from less than one month to one year after the medication is initiated.
 - ⇒ the effect of antimalarials on trans-glutaminase activity leads to stimulation of epidermal proliferation
 - ⇒ beta blockers is more common than ACEi

Management

Topical potent corticosteroid + vitamin D analogue is first-line for chronic plaque psoriasis

Management of chronic plaque psoriasis

- regular emollients may help to reduce scale loss and reduce pruritus
- First-line:
 - potent corticosteroid applied once daily <u>plus</u> vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- Second-line:
 - ⇒ if no improvement after 8 weeks then offer a vitamin D analogue twice daily
- Third-line:
 - if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a coal tar preparation applied once or twice daily

· short-acting dithranol can also be used

Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms
- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g.
 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

What should I know about vitamin D analogues?

- · examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- · adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- · they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

Scalp psoriasis

Scalp psoriasis - first-line treatment is topical potent corticosteroids

- First line
 - ⇒ potent topical corticosteroids used once daily for 4 weeks
 - ⇒ if no improvement after 4 weeks go to second line
- Second line
 - ⇒ use different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or
 - ⇒ topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

Face, flexutal and genital psoriasis

Flexural psoriasis - topical steroid

 mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

eg: clobetasone butyrate once a day

Secondary care management

Phototherapy

- narrow band ultraviolet B-light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

Systemic therapy

- Indications
 - ⇒ topical are not effective and
 - ⇒ person is impacted physically, psychologically, or socially by the problem **and**
 - ⇒ one or more of the following apply:
 - extensive psoriasis (eg, > 10% of body surface area affected or a PASI score of > 10) or
 - localised psoriasis and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) or
 - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

Methotrexate

- Oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- Ciclosporin
 - ⇒ Offer ciclosporin as the first choice in patients who need rapid or short-term disease control (for example a
 - psoriasis flare
 - palmoplantar pustulosis
 - or considering conception (both men and women) and systemic therapy cannot be avoided.
 - ⇒ Consider changing from methotrexate to ciclosporin (or vice-versa) when response
 to the first-choice systemic treatment is inadequate.
- Systemic retinoids (acitretin)
 - ⇒ if methotrexate and ciclosporin are not appropriate or have failed or
 - ⇒ for people with pustular forms of psoriasis.
- biological agents: infliximab, etanercept and adalimumab
 - ➡ In situation with uncontrolled psoriasis and psoriatic arthritis, early instigation of a biological is recommended.
 - ⇒ TNF alpha is a pro-inflammatory cytokine closely linked to the severity of psoriasis, and etanercept, a TNF alpha antagonist is the most appropriate intervention.
 - ⇒ Tuberculosis and viral hepatitis should be ruled out prior to starting therapy.
 - ⇒ Brodalumab is an anti-IL17 monoclonal antibody which has completed registration trials for psoriasis. It's likely to be reserved however for patients who fail to gain control on other interventions.
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials
 - ⇒ it is not an anti- TNF agent (so did not reactivate TB)
 - ⇒ side effects:
 - common → dental infection
 - uncommon → depression and injection site reaction

Mechanism of action of commonly used drugs:

- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- · dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

Contra-indication:

• Oral steroids are contraindicated in psoriasis and although one may see an initial improvement, a very serious rebound effect may be seen.

Question:

An elderly man with learning difficulties, is admitted to hospital with an acute exacerbation of congestive cardiac failure and severe raised plaques of psoriasis covering his chest, elbows, knees and scalp. he has been treating it with topical creams for years but has seen no improvement. What treatment would you recommend for his psoriasis?

→ Refer for PUVA

- The safest treatment that which produces the best clinical effect with minimal side effects in this patient - would be psoralen and ultraviolet light (PUVA).
- Emollients, baths and use of methotrexate require a fair amount of input from the patient in order to be effective and safe, which may not be the best option in this man.

MRCPUK-part-1-sep 2017: Which medication is of most concern with respect to worsening of psoriasis?

Atenolol

Psoriasis: guttate

- Guttate psoriasis is more common in children and adolescents.
- It may be precipitated by a streptococcal infection 2-4 weeks prior to the lesions appearing

Features

• tear drop 'drop-like' papules on the trunk and limbs

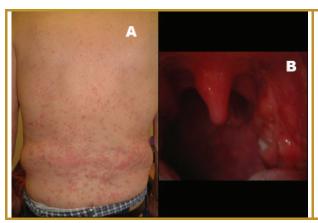


Management

- if lesions are not widespread (<10% body surface area) and the person is not impacted physically, psychologically, or socially by the problem:
 - ⇒ No treatment required
 - most cases resolve spontaneously within 2-3 months
- If the lesions are not widespread (<10% body surface area) and treatment is desired:
 - ⇒ topical agents as per psoriasis.
- If lesions are widespread (>10% body surface area):
 - ⇒ refer urgently to a dermatologist as phototherapy (UVB phototherapy) can be considered.
- with recurrent episodes → referral to ENT should be considered → tonsillectomy may be necessary
- Although guttate psoriasis can be triggered by an acute sore throat, it is not recommended to treat guttate psoriasis with anti-streptococcal antibiotics.

Differentiating guttate psoriasis and pityriasis rosea

	Guttate psoriasis	Pityriasis rosea
Prodrome	Classically preceded by a streptococcal sore throat 2-4 weeks	Many patients report recent respiratory tract infections but this is not common in questions
Appearance	'Tear drop', scaly papules on the trunk and limbs	Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions. May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance
Treatment / natural history	Most cases resolve spontaneously within 2-3 months Topical agents as per psoriasis UVB phototherapy	Self-limiting, resolves after around 6 weeks



Guttate psoriasis

- A 46-year-old man presents with an extensive pruritic rash shown in picture A.
- Two weeks previously he had a sore throat with the appearance shown in picture B.

Pyoderma gangrenosum



Overview

- Pyoderma gangrenosum typically is an expanding ulcer with a polycyclic or serpiginous outline and a characteristic undermined bluish edge.
- The pathogenesis is unknown, and is presumed to be immunological.

Features

- typically on the lower limbs
 - ⇒ It is most common on the lower limb and in scars or sites of previous trauma.
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

Causes

- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's
 - $\, \Rightarrow \,$ Estimates of the prevalence in inflammatory bowel disease (IBD) range between 2% and 5%.
 - It tends to be associated with colonic involvement and is perhaps slightly more common in patients with UC.
- · rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

Management

- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

Scabies



- Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact.
- It typically affects children and young adults.
- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

Features

- widespread pruritus
 - ⇒ Scabies can present with an itchy dermatitic-looking rash on the body, but the clues are at certain sites (soles, genitalia, buttocks)
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
 - Burrows (linear crusted lesions of a few millimetres in length) are pathognomonic
 - ⇒ It has a predilection for the web-spaces and around the nipples.
- in infants the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

Management

- permethrin 5% is first-line
- malathion 0.5% is second-line
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)

- permethrin cream doesn't have any direct effect on the pruritis itself but helps to settle symptoms indirectly by killing the mite, which is the root cause.
- You should counsel your patients that it may take longer for the itching to settle as the allergic reaction to the mite abates
- the cream should be applied everywhere below the neck, not merely where there is rash
 present.
- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation.

Patients should be given the following instructions:

- · apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and leave on the skin for 8-12 hours for permethrin, or for 24 hours for malathion, before washing off

- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- repeat treatment 7 days later

Crusted (Norwegian) scabies

- Crusted scabies is seen in patients with suppressed immunity, especially HIV.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- Ivermectin is the treatment of choice and isolation is essential

Seborrhoeic dermatitis

- Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an
 inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called
 Malassezia furfur (formerly known as Pityrosporum ovale).
- It is common, affecting around 2% of the general population

Features

- eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- otitis externa and blepharitis may develop

Associated conditions

- HIV
 - ⇒ in patients with HIV the prevalence of seborrheic dermatitis may be as high as 80%.
 - ⇒ the most useful next step → HIV testing
- Parkinson's disease

Scalp disease management

- Dandruff is an uninflamed form of seborrheic dermatitis and presents as scaly patches scattered within hair-bearing areas of the scalp.
- over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- the preferred second-line agent is ketoconazole
- selenium sulphide and topical corticosteroid may also be useful

Face and body management

Seborrhoeic dermatitis - first-line treatment is topical ketoconazole

- · topical antifungals: e.g. Ketoconazole
- topical steroids: best used for short periods
- difficult to treat recurrences are common

Skin disorder in pregnancy

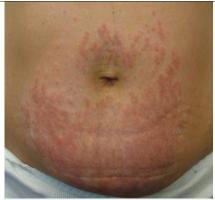
Polymorphic eruption of pregnancy

Polymorphic eruption of pregnancy is not associated with blistering

- also known as Pruritic Urticarial Papules and Plagues of Pregnancy (PUPPP)
- · pruritic condition associated with last trimester
- · lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used







Polymorphic eruption of pregnancy

Pemphigoid gestationis

Definition

bullous disorder that typically develops in the second or third trimester, beginning with urticarial lesions and blisters on the anterior abdominal wall surrounding the umbilicus.

Features

- ⇒ pruritic blistering lesions
- ⇒ often develop in peri-umbilical region, later spreading to the trunk, back, buttocks
 and arms
- ⇒ usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy

Diagnosis

⇒ A perilesional skin biopsy demonstrating linear C3 deposition at the dermoepidermal junction would confirm the diagnosis.

Treatment

⇒ oral corticosteroids are usually required





Pemphigoid gestationis

Pemphigoid gestationis

Melasma

- Melasma is a benign but relatively common skin condition which can appear in pregnancy.
- it may resolve a few months after delivery.

Chloasma

Overview

- ⇒ Chloasma is a hormonally stimulated increase in melanogenesis that mainly appears on the face.
- ⇒ The pigment is augmented by sunlight
- ⇒ On testing, levels of melanocyte-stimulating hormone are normal
- ⇒ more likely to occur in women with darker skin tones

Causes

- ⇒ Pregnancy
- ⇒ combined oral contraceptive pill

- ⇒ The pigmentation may take many months to resolve after parturition or pill discontinuation
- ⇒ avoid prolonged sunlight exposure or to use a sunblock

Skin disorders associated with tuberculosis

Possible skin disorders

- lupus vulgaris (accounts for 50% of cases)
- ervthema nodosum
- scarring alopecia
- scrofuloderma: breakdown of skin overlying a tuberculous focus
- verrucosa cutis
- gumma

Lupus vulgaris

- the most common form of cutaneous TB seen in the Indian subcontinent.
- Cutaneous TB usually occurs due to spread from an endogenous source
- It generally occurs on the face and is common around the nose and mouth.
 - ⇒ more than 80% of cases occur on the face and neck.
- The initial lesion is an erythematous flat plaque which gradually becomes elevated and may ulcerate later

- Diagnosis: On diascopy, it shows characteristic "apple-jelly" color. Biopsy will reveal tuberculoid granuloma with few bacilli. Mantoux test is positive.
- Treated with combination of drugs used for tuberculosis, such as Rifampicin, Isoniazid and Pyrazinamide (with either streptomycin or ethambutol)

Spider nevi

- · most common on the face and upper chest.
- typically asymptomatic
- usually resolve spontaneously.
- Causes
 - ⇒ chronic liver disease
 - the presence of more than five lesions is likely to be due to chronic liver disease.
 - may resolve when liver function increases or when a liver transplant is performed.
 - the cause of the spider nevi → patients cannot metabolize circulating <u>estrogen</u>
 - ⇒ pregnancy
 - may resolve after childbirth.
 - ⇒ oral contraceptives,
 - may resolve after stopping the contraceptives.



forehead lesion (spider nevus (nevus araneus))

Tinea

- Tinea is a term given to dermatophyte fungal infections.
- Three main types of infection are described depending on what part of the body is infected
 - 1. tinea capitis scalp
 - 2. tinea corporis trunk, legs or arms
 - 3. tinea pedis feet

Tinea capitis (scalp ringworm)

- a cause of scarring alopecia mainly seen in children
- if untreated a raised, pustular, spongy/boggy mass called a kerion may form
- Causes
 - → most common cause is Trichophyton tonsurans in the UK and the USA (>90% of cases)
 - ⇒ may also be caused by *Microsporum canis* acquired from cats or dogs
- Diagnosis:

- ⇒ the most useful investigation is scalp scrapings
- ⇒ lesions due to Microsporum canis green fluorescence under Wood's lamp (but do not fluoresce if caused by Trichophyton tonsurans.). lesions due to Trichophyton species do not readily fluoresce under Wood's lamp
- Management (based on CKS guidelines): oral antifungals:
 - ⇒ Terbinafine for *Trichophyton tonsurans* infections
 - Although not licensed in young children, a four-week course of the <u>fungicidal</u> drug terbinafine is often preferred.
 - ⇒ griseofulvin for *Microsporum* infections.
 - Griseofulvin is fungistatic, so a prolonged course of 2-4 months is required.
 - ⇒ Topical ketoconazole shampoo should be given for the first two weeks to reduce transmission



Image showing a kerion

griseofulvin

The enzyme that is most likely induced by griseofulvin requires which of the following cofactors?

- **Vitamin B₆**
 - Griseofulvin is a microtubule poison that is used to treat skin and nail dermatophytoses
 - strong inducer of cytochrome P450 enzymes.
 - CYP450 enzymes require heme for proper function, and thus inducers of CYP450 increase heme synthesis.

Tinea corporis (ringworm)

- causes include *Trichophyton rubrum* and *Trichophyton verrucosum* (e.g. From contact with cattle)
- well-defined annular, erythematous lesions with pustules and papules
- · may be treated with oral fluconazole



Tinea pedis (athlete's foot)

- characterised by itchy, peeling skin between the toes
- · common in adolescence

Tinea incognito

- · What is the cause for tinea incognito?
 - ⇒ Inappropriate treatment with steroid cream
- Tinea incognito is the name given to tinea when the clinical appearance has been altered by inappropriate treatment, usually a topical steroid cream
- The result is that the original infection slowly extends Often the patient and/or their doctor believe they have a dermatitis, hence the use of a topical steroid cream
- The steroid cream dampens down inflammation so the condition feels less irritable But when the cream is stopped for a few days the itch gets worse, so the steroid cream is promptly used again
- The more steroid applied, the more extensive the fungal infection becomes

Vitiligo

Definition

 Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin.

Epidemiology

- It is thought to affect around 1% of the population
- symptoms typically develop by the age of 20-30 years.

Features

- well demarcated patches of depigmented skin
- · the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

Associated conditions

- · type 1 diabetes mellitus
- · Addison's disease
- autoimmune thyroid disorders
- · pernicious anaemia
- alopecia areata

Diagnosis

- · Diagnosis is made clinically
- anti-melanocyte antibodies
- · can be confirmed using a skin biopsy.

Management

- sun block for affected areas of skin
- camouflage make-up
- topical corticosteroids may reverse the changes if applied early
- there may also be a role for topical tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients





Vitiligo

Angular stomatitis

- Angular stomatitis describes erythema and fissuring of the skin adjacent to the angle of the mouth.
- The most common cause is Candida infection
- also associated with:
 - ⇒ allergy,
 - ⇒ seborrhoeic dermatitis.
 - ⇒ vitamin B deficiencies,
 - ⇒ iron deficiency.

Venous ulceration

- Venous ulcers are secondary to venous stasis and chronic stretching of the walls of the superficial veins. These eventually become thinner and ulcerate.
- · typically seen above the medial malleolus

The incidence of venous leg ulceration is higher in:

- · obese patients
- history of varicose veins
- history of deep vein thrombosis

Ulcers occur owing to:

- venous stasis
- · secondary increase in capillary pressure
- fibrosis
- poorly nourished skin particularly over areas such as the medial malleolus

Investigations

- ankle-brachial pressure index (ABPI) is important in non-healing ulcers to assess for poor arterial flow which could impair healing
 - ⇒ a 'normal' ABPI may be regarded as between 0.9 1.2.
 - ⇒ Values below 0.9 indicate arterial disease.
 - ⇒ Interestingly, values above 1.3 may also indicate arterial disease, in the form of false-negative results secondary to arterial calcification (e.g. In diabetics)

Management

Management of venous ulceration - compression bandaging

- compression bandaging, usually four layer (only treatment shown to be of real benefit)
- The mainstay of treatment of venous ulceration is compression therapy, which aims to improve venous return and thereby reduce venous hypertension.
- The patient should always have their Doppler's and ABPI (ankle brachial pressure index)
 prior to compression. The ABPI should be greater than 1 before compression bandaging is
 used (this excludes significant arterial disease.
- · oral pentoxifylline, a peripheral vasodilator, improves healing rate
- · small evidence base supporting use of flavinoids
- little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression

Pressure ulcers

Waterlow score - used to identify patients at risk of pressure sores

Overview

- Pressure ulcers develop in patients who are unable to move parts of their body due to illness, paralysis or advancing age.
- They typically develop over bony prominences such as the sacrum or heel. The following factors predispose to the development of pressure ulcers:
 - ⇒ malnourishment
 - ⇒ incontinence
 - □ lack of mobility
 - ⇒ pain (leads to a reduction in mobility)
- The Waterlow score is widely used to screen for patients who are at risk of developing
 pressure areas. It includes a number of factors including body mass index, nutritional
 status, skin type, mobility and continence.

Grading of pressure ulcers

the following is taken from the European Pressure Ulcer Advisory Panel classification system.

Grade	Findings	
Grade 1	Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin	
Grade 2	Partial thickness skin loss involving epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister	
Grade 3	Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia.	
Grade 4	Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss	

Management

- a moist wound environment encourages ulcer healing. Hydrocolloid dressings and hydrogels may help facilitate this. The use of soap should be discouraged to avoid drying the wound
- wound swabs should not be done routinely as the vast majority of pressure ulcers are
 colonised with bacteria. The decision to use systemic antibiotics should be taken on a
 clinical basis (e.g. Evidence of surrounding cellulitis)
- · consider referral to the tissue viability nurse
- surgical debridement may be beneficial for selected wounds

Keloid scars

Keloid scars are most common on the sternum

Keloid scars are tumour-like lesions that arise from the connective tissue of a scar and extend beyond the dimensions of the original wound

Predisposing factors

Keloid scars - more common in young, black, male adults

- ethnicity: more common in people with dark skin
- occur more commonly in young adults, rare in the elderly
- common sites (in order of decreasing frequency): sternum, shoulder, neck, face, extensor surface of limbs, trunk
- Keloid scars are less likely if incisions are made along relaxed skin tension lines*
 - *Langer lines were historically used to determine the optimal incision line. They were based on procedures done on cadavers but have been shown to produce worse cosmetic results than when following skin tension lines

Treatment

- early keloids may be treated with intra-lesional steroids e.g. triamcinolone
- · excision is sometimes required

Increased skin fragility

- Increased skin fragility is seen in a number of disorders and is used as a clinical test in bullous disorders (Nikolsky's sign).
- · Other causes include:
 - ⇒ pemphigus vulgaris
 - ⇒ porphyria cutanea tarda
 - ⇒ drug reactions (especially pseudoporphyria).
- Other causes of increased skin fragility (not associated with bullae) include:
 - ⇒ long term corticosteroid therapy,
 - ⇒ Ehlers-Danlos syndrome
 - ⇒ curvy (vitamin C deficiency).

Basal cell carcinoma (BCC)

Overview

- Basal-cell carcinomas are the most common malignant skin tumour and are related to excessive sun exposure
 - ⇒ most commonly occurs in elderly patients with sun-damaged skin.
- · Lesions are also known as rodent ulcers
- characterised by slow-growth and local invasion. Metastases are extremely rare.
- . BCC is the most common type of cancer in the Western world.
- BCC is more commonly seen on the <u>upper</u> lip.

Genetics

- environmental and genetic factors are believed to predispose patients to BCC
- Basal cell carcinoma is associated with mutations in the Hedgehog signaling pathway.
- Up to 70% of people with sporadic BCC without Gorlin syndrome have patched PTCH1 gene mutations as a result of UV radiation exposure.

Features

- many types of BCC are described. The most common type is nodular BCC.
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia
- may later ulcerate leaving a central 'crater'
- characterized histologically by <u>palisading</u> nuclei.
 - ⇒ Palisading nuclei consist of parallel rows of <u>elongated</u> nuclei.

Management

- surgical removal
 - ⇒ Mohs surgery for is useful for minimizing the amount of safety margin excised.
- curettage
- cryotherapy
- topical cream: imiquimod, 5- fluorouracil
- radiotherapy



BCC VS SCC

Basal cell carcinoma	Squamous cell carcinoma
Most common	2 nd most common
Present in upper part of face	Present in lower part of face (appear most often on the lower lip, ear, and nose.)
Does not metastasize and kill by local invasion(rodent ulcer)	Can metastasize
presents as a " pearly " papule or nodule that grows slowly with shiny appearance with telangiectasias and an umbilicated center or ulcer	usually hyperkeratotic scaly lesion with crusting and ulceration. often well-defined, superficial, discrete, and hard lesions arising from an indurated, rounded, and elevated base

Squamous cell carcinoma (SCC)

Overview

- SCC is the second most common non-melanoma skin cancer worldwide (after basal cell cancer).
- SCC is the most common oral cancer.
- More common in elderly males.
- It is possible to get SCC on any part of the body, including the inside of the mouth, lips, and genitals.
- Women frequently get SCC on their lower legs.

Precursor and variants of SCC:

- Actinic keratosis presents as hyperkeratotic grey-white plaques and is a precursor lesion to squamous cell carcinoma of the skin.
 - ⇒ Precursor lesions for SCCs are called actinic (or sun-damage) keratosis

• **Keratoacanthoma** is a cup-shaped form of squamous cell carcinoma of the skin that develops rapidly and resolves spontaneously.

Risk factors

- photo-exposed skin such as face and lower lips.
 - often caused by ultraviolet B-light, which can mutate DNA via the formation of pyrimidine dimers.
 - ⇒ exposure to ultraviolet radiation (UV), especially UVB → Mutations in the
 p53 tumour suppression gene
 - ⇒ commonly affects the lower lip.
- The incidence of skin cancer has been increasing among Caucasians but remains relatively low in people of color.
 - ⇒ Light-skinner, non-Hispanic white populations experience higher rates of SCC than darker people of color.
 - ⇒ Low incidence in darker skins due to photo-protection provided by increased epidermal melanin, which filters twice as much ultraviolet (UV) radiation
 - ⇒ When skin cancer occurs in **people of color**, patients often present with an advanced stage, and thus, **worse prognosis** in comparison to Caucasian patients
- Chronic immunosuppression
 - ⇒ more common in patients who have received an organ transplant.
- old scars or burns
 - ⇒ may arise from areas of Bowen's disease and sometimes in the margin of a chronic leg ulcer.
 - ⇒ (SCC) arising on a scar is termed a Marjolin ulcer.
 - Marjolin ulcer is typically aggressive and associated with a poor prognosis.
- · arsenic exposure
- ionizing radiation
- HPV infection
- chronic infections, particularly those associated with chronically draining sinuses.
- · actinic keratoses and Bowen's disease
- Inherited syndromes: eg: xeroderma pigmentosum and albinism
- smoking

Features

usually appears as a scaly or crusty area of skin, with a red, inflamed base.

Diagnosis

- Excision biopsy is essential for accurate diagnosis.
 - ⇒ shows keratin pearl appearance.
 - ⇒ The presence of **keratin pearls** indicates that the tumor is well-differentiated and **carries a better prognosis**.
 - undifferentiated tumor would contain almost entirely atypical cells that have lost their keratin producing function and thus keratin pearls would be absent.

Treatment

- Treatments include non-surgical destruction (e.g., using cryotherapy), topical chemotherapy, traditional surgical excision, and Mohs micrographic surgery.
- Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then
 margins should be 6mm.
- Mohs surgery is the best surgical treatment to minimize the loss of normal tissue.
- Radiotherapy is the treatment of choice in patients who are poor surgical candidates.
- Chemotherapy is used as adjuvant therapy in high risk patients

Prevention

Sunscreen is used to minimize risk of developing SCC.

Prognosis

Good Prognosis	Poor prognosis
Well differentiated tumours	Poorly differentiated tumours
<20mm diameter	>20mm in diameter
<2mm deep	>4mm deep
No associated diseases	Immunosupression for whatever reason

Keratoacanthoma (KA)





Overview

- Keratoacanthoma (KA) is a relatively common low-grade malignancy that originates in the pilosebaceous glands and resembles squamous cell carcinoma (SCC) pathologically.
- Some experts support classifying KA as a variant of invasive SCC.
- Keratoacanthoma is a benign epithelial tumour.
- It is believed to develop from the hair follicle.
- · more common in males.
- They are more frequent in middle age and do not become more common in old age (unlike basal cell and squamous cell carcinoma)
- KA is characterised by rapid growth over a few weeks to months, followed by spontaneous resolution over four to six months in most cases.
- Lesions typically are solitary and begin as firm, roundish, skin-coloured or reddish papules
 that rapidly progress to dome-shaped nodules with a smooth shiny surface and a central
 crateriform ulceration or keratin plug that may project like a horn.

Features - said to look like a volcano or crater

- initially a smooth dome-shaped papule
- rapidly grows to become a crater centrally-filled with keratin

Treatment

- The most suitable management → Urgent referral to dermatology
- Spontaneous regression of keratoacanthoma within 3 months is common, often resulting in a scar.
- Should be urgently excised as it is difficult clinically to exclude squamous cell carcinoma.
 Removal also may prevent scarring.

Actinic keratoses

Overview

- Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure
- Less than 10% of actinic keratoses progress to invasive squamous cell carcinoma.

Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present

Management

- prevention of further risk: e.g. sun avoidance, sun cream
- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- · topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- · curettage and cautery

Malignant melanoma

Overview

- Melanocytes are positioned in the basal layer of the epidermis
- Melanoma is the third most common skin cancer, but is the most common cause of skin cancer-related death.
- Up to 20% of patients develop metastatic disease.

The mnemonic of ABCDE regarding characteristics of a melanoma are as follows:

- A Asymmetry one half of the lesion does not match the other half
- **B** Border irregularity
- C Colour variegation pigmentation is not uniform
- D Diameter- a diameter 7 mm warrants investigation although changes in size are also important
- E Evolution evolving size or changes in characteristics such as nodules.

Prognostic factors

Melanoma: the invasion depth of the tumour is the single most important prognostic factor

The invasion depth of a tumour (Breslow depth) is the single most important factor in determining prognosis of patients with malignant melanoma

Breslow Thickness	Approximate 5 year survival
< 1 mm	95-100%
1 - 2 mm	80-96%
2.1 - 4 mm	60-75%
> 4 mm	50%

Treatment

 Vemurafenib is a small molecule inhibitor of BRAF oncogene that can be found in melanoma. As such, Vemurafenib is used to treat metastatic melanoma.

Lentigo maligna

- Lentigo maligna is a type of melanoma in-situ.
- It typically <u>progresses slowly</u> but may at some stage become invasive causing lentigo maligna melanoma.
- Lentigo maligna melanoma occurs on the sun-exposed skin areas (usually the face) of elderly patients

Acral lentiginous melanoma

- The acral lentiginous melanoma is normally seen on the sole of the foot, and occasionally on the palm of the hand
- It is characterised by a raised darker area surrounded by a paler macular (lentiginous) area that may extend for several centimetres around the raised area
- There are two clinical <u>clues that lead us to suspect this diagnosis</u>: the patient's race and the location of the lesion.
 - Acral lentiginous melanoma is more common in <u>African-Americans</u> and Asians than other forms of melanoma.
 - the lesion is located in an <u>area not exposed to sunlight</u> (the sole of the foot is the most common place for this type of melanoma).

Other notes

- Patients with a strong family history of melanoma are more likely to harbor a mutation in the cyclin-dependent kinase inhibitor 2A tumor-suppressor gene (CDKN2A mutation) that codes for p16, which prevents progression through G1.
- Periungual melanomas occur in the area of the nailbed
- Hutchinson's sign (brown pigmentation on the nailfold) is an important pointer to malignant melanoma
- Superficial spreading melanoma is the commonest type, consisting of an irregular brown, black or blue—black lesion with some intermingled inflammation
- Nodular melanoma:
 - ⇒ the most <u>rapidly growing and aggressive variant</u> and may contain relatively little melanin pigment
 - ⇒ associated with higher rates of metastasis and **poorer outcomes** than classic melanoma.

Moles

 Uniform pigmentation is not in itself a suspicious feature of a mole, but colour variegation and irregular border are two of many suspicious features.

Systemic mastocytosis

Results from a neoplastic proliferation of mast cells

Features

- urticaria pigmentosa produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- monocytosis on the blood film

Diagnosis

- · raised serum tryptase levels
- · urinary histamine

Angiosarcoma

- Angiosarcomas are malignant vascular tumours most commonly seen in elderly men.
- most commonly occur on the scalp and forehead.
- present an infiltrative vascular patch or plaque with super-imposed nodules which may bleed with minor trauma.
- · poor prognosis.
- Angiosarcomas can also occur in areas of chronic lymphoedema.



Pyogenic granuloma



Overview

- relatively common benign skin lesion
- benign vascular lesion of the skin and mucosa.
- The name is a double misnomer the lesion is neither pyogenic nor a granuloma.
- There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.
- Pathologically, it is an inflammatory lesion composed of granulation tissue and chronic inflammatory cells.

Etiology

- unknown
- associated with trauma and pregnancy

Epidemiology

· more common in women and young adults

Features

- initially soft, round, bright red spot
- · usually solitary lesions,
- Lesions often grow rapidly (<u>over weeks</u>),
- tender and bled easily when touched.

Localization

- The most common location are:
 - ⇒ fingers (commonly involve the digits)
 - ⇒ mucosal surfaces of the mouth
 - ⇒ inner surfaces of the nose.

Treatment

- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist.
- surgical excision
 - ⇒ Removal methods include curettage and cauterisation, cryotherapy, excision





Skin disorders associated with malignancy Paraneoplastic syndromes associated with internal malignancies:

Skin disorder	Associated malignancies
Acanthosis nigricans	Gastric cancer
Acquired ichthyosis	Lymphoma
Acquired hypertrichosis lanuginosa	Gastrointestinal and lung cancer
Dermatomyositis	Ovarian and lung cancer
Erythema gyratum repens	Lung cancer
Erythroderma	Lymphoma
Migratory thrombophlebitis	Pancreatic cancer
Necrolytic migratory erythema	Glucagonoma
Pyoderma gangrenosum (bullous and non-bullous forms)	Myeloproliferative disorders
Sweet's syndrome	Haematological malignancy e.g. Myelodysplasia - tender, purple plaques
Tylosis	Oesophageal cancer

Acrokeratosis paraneoplastica

A widespread psoriatic-type rash involving the ears is suggestive of acrokeratosis paraneoplastica.

- Most acrokeratosis paraneoplastica cases are associated with squamous cell carcinoma
 of the upper one third of the respiratory or GI tract, i.e. the oropharynx, larynx, lungs or
 oesophagus.
 - The symptoms of indigestion and food sticking fit best with a diagnosis of oesophageal carcinoma.

Otitis externa

Otitis externa is a common reason for primary care attendance in the UK.

Causes of otitis externa include:

- infection: bacterial (Staphylococcus aureus, Pseudomonas aeruginosa) or fungal
- · seborrhoeic dermatitis
- contact dermatitis (allergic and irritant)

Features

- · ear pain, itch, discharge
- · otoscopy: red, swollen, or eczematous canal

Management

- Initial management
 - ⇒ topical antibiotic or a combined topical antibiotic with steroid
 - if the tympanic membrane is perforated aminoglycosides are traditionally not used. many ENT doctors disagree with this and feel that concerns about ototoxicity are unfounded
 - ⇒ if there is canal debris then consider removal
 - ⇒ if the canal is extensively swollen then an ear wick is sometimes inserted

Second line options include

- ⇒ consider contact dermatitis secondary to neomycin
- ⇒ oral antibiotics if the infection is spreading
- ⇒ taking a swab inside the ear canal
- ⇒ empirical use of an antifungal agent

Malignant otitis externa

- ⇒ more common in elderly diabetics.
- ⇒ In this condition there is extension of infection into the bony ear canal and the soft tissues deep to the bony canal.
- ⇒ Intravenous antibiotics may be required.

Livedo reticularis (LR)

Definition

 A vascular syndrome that can be caused by either benign autonomic dysregulation of cutaneous perfusion or pathological obstruction of blood vessels.

Pathophysiology

Physiological livedo (idiopathic livedo): primary livedo

- ⇒ Autonomic dysregulation (functional disturbance) causing slowed cutaneous perfusion in response to external factors (i.e., cold). Triggered by cold, regresses after application of warmth.
- Pathological livedo (livedo racemosa): secondary livedo
 - ⇒ Localized obstructions slow the blood flow (organic disturbance). Persists after warming the skin.

Features

- Patchy, reticulated, vascular network with a red-blue or violaceous discoloration of the skin.
- A "fish-net like" mottling of the skin
- Occur more in women than in men and usually in the 3rd decade of life.
- Occurs most often in the lower extremities





Causes

It is mainly idiopathic (primary livedo reticularis is the most common cause)

Causes Secondary livedo reticularis:

- Obstruction / vasculopathy
 - ⇒ Antiphospholipid syndrome
 - Livedo racemosa is the most common dermatologic presentation in patients with antiphospholipid syndrome (APS), presenting in 25% of patients with primary APS and in 70% of patients with SLE-associated APS.
 - ⇒ Cryoglobulinaemia
 - ⇒ Polycythaemia rubra vera
 - ⇒ Multiple myeloma
 - ⇒ Cold agglutinin disease
 - ⇒ Protein C and S deficiency
 - ⇒ Antithrombin III deficiency
 - ⇒ Disseminated intravascular coagulation
 - ⇒ Haemolytic uraemic syndrome
 - ⇒ Emboli (DVT, cholesterol emboli and septic emboli)
 - ⇒ Hypercalcaemia (calcium deposits)
 - ⇒ Infections (syphilis, tuberculosis, Lyme disease)
- Autoimmune / vasculitis / connective tissue disease
 - ⇒ Small, medium and large vessel vasculitis.
 - ⇒ SLE
 - ⇒ Dermatomyositis
 - ⇒ Rheumatoid arthritis
 - ⇒ Polyarteritis nodosa

Drugs

- Amantadine (dopamine agonist used to treat Parkinson disease) causes livedo through arteriolar vasospasm provoked by catecholamines.
- Associations
 - ⇒ LR preceded the onset of repeated attacks of pancreatitis in a patient with chronic pancreatitis.
 - ⇒ Primary fibromyalgia
 - ⇒ Congenital hypogammaglobulinemia.

Treatment

- Physiological: warmth. bath PUVA is a therapeutic option with the possibility of some success.
- · Pathological: treat underline cause

Livedo reticularis that does not regress after application of warmth is indicative of an underlying vascular disease and requires treatment.

Hyperhidrosis describes the excessive production of sweat

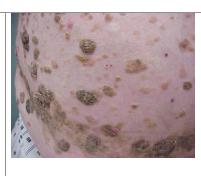
Management options include

- topical aluminium chloride preparations are first-line. Main side effect is skin irritation
- iontophoresis: particularly useful for patients with palmar, plantar and axillary hyperhidrosis
- botulinum toxin: currently licensed for axillary symptoms
- surgery: e.g. Endoscopic transthoracic sympathectomy. Patients should be made aware of the risk of compensatory sweating

Seborrheic keratosis

- Seborrheic keratoses are the most common benign tumor in older individuals.
- and they develop from the proliferation of epidermal cells.
- No specific etiologic factors have been identified.
- Typical features include a warty and waxy surface with surface crypts and a stuck on appearance.
- They typically have an appearance of being stuck on the skin surface.
- Because they begin at a later age and can have a wart-like appearance, seborrheic keratoses are often called the "barnacles of aging.
- · Most commonly they are several
- Can growths anywhere on the skin, except the palms and soles. Most often on the chest, back, head, or neck.
- Commonly used treatments include Curettage and cautery (C&C), and cryotherapy (for thinner lesions).





multiple seborrheic keratoses in an autosomally dominant mode of inheritance.

Solar keratosis

- hyperkeratotic lesion with underlying erythema.
- · bleed when scratched
- · Progression of these lesions to squamous cell skin cancer is slow
- Topical 5-FU cream used twice a day for 3-4 weeks usually achieves clearance of the lesion.
- Diclofenac gel requires a more prolonged treatment period (up to 12 weeks), meaning that
 it is the second-choice option for compliance reasons. It is useful where coverage of a
 larger area of skin is required.



solar keratosis (on scalp of elderly)

Telogen phase

- The telogen phase is the resting phase of the hair follicle.
- Due to extreme stress → shedding of hair leading to loss of thickness → loss of hair.
- It occurs as a normal phenomenon one to three months after pregnancy.
- No treatment is required (only reassurance) and hair thickness eventually recovers without further intervention.

Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Psychiatry

Updated

Unexplained symptoms

Unexplained symptoms

- Somatisation = Symptoms
- hypoChondria = Cancer
- · Conversion disorder
 - typically involves involuntary loss of motor or sensory function without a physiologic cause, often following an acute stressor.
- · Dissociative disorder
 - involves psychiatric symptoms e.g. Amnesia, fugue, stupor
- Malingering patients consciously fake or exaggerate for secondary gain, such as money, sick leave, or avoidance of responsibilities.
- · Somatisation disorder

Eating disorders: Anorexia nervosa

Definition

Anorexia nervosa is an eating disorder characterised by an intense fear of gaining weight
and distorted body image resulting in calorie restriction and severe weight loss leading to
inappropriately low body weight (BMI < 18.5 kg/m2), with the inability to recognize the
seriousness of their significantly low body weight.

Subtypes

Restricting type	Binge-eating/purging type	
 No binge eating or purging over a 3-month period weight loss is achieved by excessive dieting, exercise, or fasting 	 Presence of binge eating or purging over a 3-month period weight loss is achieved by vomiting, diuretic and laxative abuse, or enemas 	

Features

- Significant low BMI < 18.5 using strategies that include restrictive eating, purging, and excessive exercise
- · Fear of weight gain
- · Lack of awareness of the seriousness of low body weight
- Distorted body image and believe they are "fat" when they usually are very thin.
 - ⇒ Use of laxatives to drive weight loss is common, and a purgative screen is therefore a logical next step.

Complications (due to weight loss & malnutrition)

- Endocrine:
 - ⇒ central hypogonadism (Hypothalamic suppression) → estrogen deficiency → ↓ LH & FSH → estrogen deficiency leads to:
 - secondary Amenorrhea (functional hypothalamic amenorrhea)
 - osteoporosis →↑ stress fractures.
 - ⇒ Euthyroid sick syndrome, hypothyroidism

• Cardiac:

- ⇒ structural : cardiac mass, ↓cardiac chamber volumes, mitral valve prolapse, and pericardial effusion.
- ⇒ Functional: bradycardia, hypotension and QT interval prolongation. So dizziness is the most concerning symptom
- Refeeding syndrome: occur due to fluid and electrolyte shifts, marked by hypophosphatemia → arrhythmias.

Lab findings

- Electrolyte imbalances: ↓ potassium, ↓ sodium, ↓ chloride, ↓ phosphate, ↓ magnesium, ↑ bicarbonate (metabolic alkalosis)
- ↑↑ Cortisol,
- \(\gamma\) growth hormone (due to GH resistance),
- ↑↑ glucose (impaired glucose tolerance)
- Hypercholesterolaemia
- Hypercarotinaemia
- low T3 with normal T4 and TSH
- hypoalbuminaemia

Characteristic findings of Anorexia Nervosa		
General	Low BMI (<18.5 kg/m²), hypothermia	
Cardiovascular	Bradycardia, hypotension	
Gastrointestinal	Melanosis coli, dental erosions, and parotid gland hypertrophy (in binging/purging type)	
Fluids, electrolytes, and nutrition (FEN)	Dehydration, malnutrition, hypokalemia (in binging/purging type)	
Genitourinary	Secondary amenorrhea	
Musculoskeletal	Osteoporosis	
Skin	Lanugo (downy, dark hair), dry skin, erosions on dorsal knuckles (in binging/purging type)	

Differential diagnosis

- Bulimia nervosa
 - ⇒ not significantly underweight; rather, most of patients are at normal weight or overweight
 - ⇒ do not have excessive restrictive caloric intake behavior that is characteristic of patients with anorexia nervosa, so complications of starvation are unlikely

Treatment

- first-line → Cognitive behavioral therapy & Nutritional support
- second line (antipsychotic) → olanzapine
 - ⇒ Tricyclic antidepressants should not be used because of their potential cardiotoxicity.
 - ⇒ Bupropion should not be used because it is associated with a higher incidence of seizures in patients with eating disorders.
 - ⇒ Do not offer medication as the sole treatment for anorexia nervosa.

Anorexia features

- · most things low
- G's and C's raised: growth hormone, glucose, salivary glands, cortisol, cholesterol, carotinaemia

The best, most easily obtainable measure of clinical improvement in a patient with anorexia nervosa \rightarrow a weight gain of 1 pound (0.45 kg) per week.

The antidepressant bupropion lowers the seizure threshold. It is, therefore, contraindicated in individuals with eating disorders who are at an increased risk of developing seizures secondary to dehydration and electrolyte imbalances.

Eating disorders: Bulimia nervosa

Definition

 Bulimia nervosa is a type of eating disorder characterised by episodes of binge eating followed by intentional vomiting to prevent weight gain.

Features

- BMI is normal or slightly elevated (≥ 18.5 kg/m2)
- Induced vomiting \rightarrow dorsal hand calluses (Russell sign), erosion of the teeth , mallory-Weiss syndrome
- Parotid gland hypertrophy
- ↑Serum amylase
- Electrolyte disturbances (eg,↓ K+,↓ Cl−), metabolic alkalosis

Treatment

- Cognitive behavioural therapy (CBT)
- · Do not offer medication as the sole treatment for bulimia nervosa.

Parotid hypertrophy and erosion of the teeth are the most common physical signs of Bulimia nervosa and may prompt diagnosis.

Hypomania vs mania

The presence of psychotic symptoms differentiates mania from hypomania			
Mania ⇒ Psychotic symptoms	Mania and Hypomania		
delusions of grandeur	Mood Predominately elevated irritable		
Auditory hallucinations	Speech & Thought	PressuredFlight of ideasPoor attention	
	Behaviour	InsomniaLoss of inhibitions: risk-takingIncreased appetite	

Antipsychotics

Antipsychotics in the elderly - increased risk of stroke and VTE

- Antipsychotics act as dopamine D2 receptor antagonists, blocking dopaminergic transmission in the mesolimbic pathways.
- Conventional antipsychotics are associated with problematic extrapyramidal side-effects which has led to the development of atypical antipsychotics such as clozapine

Extrapyramidal side-effects

- Parkinsonism
- acute dystonia (e.g. torticollis, oculogyric crisis)
 - ⇒ affects about 2% of patients.
 - **⇒** Administer procyclidine
- akathisia (severe restlessness)
- tardive dyskinesia (late onset of choreoathetoid movements, abnormal, involuntary),
 - ⇒ may occur in 40% of patients,
 - ⇒ may be irreversible,
 - ⇒ most common is chewing and pouting of jaw

Specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

Other side-effects

- antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- sedation,
- weight gain
- raised prolactin: galactorrhoea,
 - ⇒ block dopamine D2 receptors → block dopamine's action on the pitutary → reduces inhibition of prolactin secretion → hyperprolactinaemia.
- Amenorrhoea, infertility
- loss of libido, and erectile dysfunction.
- impaired glucose tolerance
- neuroleptic malignant syndrome: pyrexia, muscle stiffness
- reduced seizure threshold (greater with atypicals)
- prolonged QT interval (particularly haloperidol)

Typical antipsychotics

Typical Antipsychotics			
High Potency Antipsychotics (in Descending Order)	Advantages	Disadvantages	Unique Features
Haloperidol	Fewer side effects	Lligh googlistics	Able to use as long-acting depot
Fluphenazine	hypotension	High association with extrapyramidal symptoms	injectionsCan be given IM in acute situations
Perphenazine			
Chlorpromazine	Lower frequency	Greater incidence of anticholinergic side-effects, hypotension, sedation	Corneal deposits
Thioridazine	of extrapyramidal side effects		Retinal depositsQT prolongation

Atypical antipsychotics

Atypical antipsychotics commonly cause weight gain

atypical antipsychotics such as olanzapine/risperidone/clozapine have been associated with hyperglycaemia and insulin resistance.

- Clozapine: Most effective anti-psychotic → Decreased suicide risk. → Agranulocytosis
- Adverse effects of atypical antipsychotics: weight gain. clozapine is associated with agranulocytosis.

Clozapine is no longer used first-line due to the risk of agranulocytosis

Risperidone is a high-affinity D2 and 5-HT-2 receptor antagonist

Neuroleptic malignant syndrome (NMS)

• It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

A patient with P/H/O parkinson's disease, deteriorate 1-2 days after admission to hospital for other condition \rightarrow neuroleptic malignant syndrome (NMS) as a result of not taking her parkinson's medication \rightarrow **do Creatine kinase to confirm the diagnosis**

- . Onset usually in first 10 days of treatment or after increasing dose
- Renal failure may occur secondary to rhabdomyolysis
- Raised creatine kinase in most cases. the most important investigation to be performed

Management

- · stop antipsychotic
- IV fluids to prevent renal failure
- dantrolene may be useful in selected cases
 - thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum
- bromocriptine, dopamine agonist, may also be used
- levodopa preparations may be beneficial

Neuroleptic malignant syndrome	Serotonin syndrome	
develops over days to weeks.	develops over 24 hours.	
 characterized by sluggish neuromuscular responses (rigidity, bradyreflexia). 	 characterized by neuromuscular hyperreactivity (tremor, hyperreflexia, myoclonus). 	
 resolution typically requires an average of nine days. 	resolution typically requires less than 24 hours .	

Serotonin syndrome

- Myoclonus is the distinguishing feature of serotonin syndrome (found only in serotonin syndrome).
- Occur in those taking therapeutic doses of SSRIs, as part of <u>drug-drug interaction</u> (e.g. the addition of: ondansetron, amphetamine, cocaine, meperidine(Pethidine), dextromethorphan, fentanyl, buspiron, ergot alkaloids, lithium, L-dopa, LSD, St. John's Wort), or following intentional self-poisoning with SSRI.
- treatment
 - stopping any serotinergic agents
 - using benzodiazepines for agitation
 - consideration of use of serotonin antagonists such as cyproheptadine if there is severe autonomic disturbance.

Antidepressants

• SSRIs are the first-line treatment for the vast majority of patients with depression

Selective serotonin reuptake inhibitors (SSRIs)

SSRI + NSAID = GI bleeding risk - give a PPI

Mechanism of action

- ⇒ inhibition of serotonin reuptake in synaptic cleft → ↑ serotonin levels
- ⇒ primarily act at the 5HT transporter protein

Drugs

- ⇒ Fluoxetine
- ⇒ Paroxetine
- ⇒ Sertraline
- ⇒ Escitalopram

Indications

- ⇒ First-line treatment for major depressive disorder
- ⇒ Generalized anxiety disorder
- ⇒ Obsessive-compulsive disorder
- ⇒ Post-traumatic stress disorder
- ⇒ Somatic symptom disorder
- ⇒ Panic disorder
- ⇒ Gambling disorder
- ⇒ Premature ejaculation
- ⇒ Premenstrual dysphoric disorder
- ⇒ Binge-eating disorder

Side effects

- ⇒ Sexual disorders (anorgasmia, erectile or ejaculatory dysfunction, ⊥ libido)
- ⇒ Diarrhea, nausea, vomiting
 - gastrointestinal symptoms are the most common side-effect
- ⇒ Sleep disorders
- ⇒ Headache
- ⇒ Increased risk of bleeding
 - proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- ⇒ Serotonin syndrome
- ⇒ Risk of suicide attempt a few days after commencing treatment with an SSRI
 - In major depressive disorder, the greatest risk for suicide occurs after a partial response to antidepressants.
 - Usually, energy and motivation return before a subjective improvement in mood occurs, and a patient who has been too apathetic to act on suicidal rumination may, at this point, attempt suicide.
- ⇒ patients should be counselled to be vigilant for <u>increased anxiety and agitation after</u>
 starting a SSRI

Contraindications

⇒ risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

Additional information

⇒ must usually be taken for 4–6 weeks before symptom reduction is seen

- ⇒ citalopram (although ↑ QT interval) and fluoxetine are currently the preferred SSRIs
- ⇒ sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants
- ⇒ nice advice 2017 → For people who also have a chronic physical health problem, consider using <u>citalopram</u> or <u>sertraline</u> as these have a lower propensity for interactions.
- ⇒ SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

Citalogram and the QT interval

- ⇒ citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with:
 - congenital long QT syndrome;
 - known pre-existing QT interval prolongation; or
 - in combination with other medicines that prolong the QT interval
- ⇒ the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

Interactions

- ⇒ NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given coprescribe a proton pump inhibitor
- ⇒ warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine
 - the SSRIs least likely to cause drug interactions with warfarin appear to be sertraline and citalopram.
- ⇒ aspirin: see above
- ⇒ triptans: avoid SSRIs
- ⇒ fluoxetine and paroxetine have a higher propensity for drug interactions

Antidepressant Follow-up

- After initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.
- ⇒ For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.
- ⇒ If a patient makes a good response to antidepressant therapy, they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.
- Selective serotonin reuptake inhibitor discontinuation syndrome

Paroxetine - higher incidence of discontinuation symptoms

- ⇒ When stopping a SSRI, the dose should be gradually reduced over a 4-week period
 - This not necessary with fluoxetine due to its longer half-life.
- ⇒ Paroxetine has a higher incidence of discontinuation symptoms.
- ⇒ SSRI withdrawal syndrome typically begins within 24-48 hours after withdrawal,
- **⇒** Discontinuation symptoms
 - Psychiatric (anxiety, insomnia, mood lability, vivid dreams)
 - Gastrointestinal (nausea, vomiting, diarrhoea cramping pain), and
 - Neurological (dizziness, headache, paraesthesia, dystonia, tremor).

Management of depression in elderly with Alzheimer's

- citalopram is the best treatment
 - ⇒ Although citalopram may have minor effects on cognition, it has been shown in patients with Alzheimer's to impact positively on patient mood and wellbeing and is associated with a significant improvement in agitation and care giver distress.
 - ⇒ Dose limitation to 20 mg is generally recommended in the elderly because of a risk of QT prolongation.
- Fluoxetine and sertraline have no significant positive effect on mood in patients with Alzheimer's disease.
- whilst valproate is of value as a mood stabiliser outside the context of Alzheimer's, it is of
 little value in patients with the condition.

while not as selective as the SSRIs, drugs of abuse such as cocaine, fenfluramine, and (3,4-methylenedioxy) methamphetamine (MDMA or ecstasy) are inhibitors of serotonin uptake.

<u>Selective serotonin-norepinephrine reuptake inhibitors</u> (SSNRIs)

- Mechanism of action
 - ⇒ inhibition of serotonin and norepinephrine reuptake in synaptic cleft
 - → ↑ serotonin and norepinephrine levels
- Drugs
 - ⇒ Venlafaxine
 - ⇒ Duloxetine
- Indications
 - ⇒ Major depressive disorder (**second-line therapy**)
 - ⇒ Generalized anxiety disorder
 - ⇒ Panic disorder
 - ⇒ Duloxetine: stress incontinence in women
- Side effects
 - ⇒ Similar profile to SSRIs (see "Selective serotonin reuptake inhibitors" above)
 - ⇒ Increased blood pressure
- Contraindications:
 - ⇒ risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
- Additional information:
 - ⇒ Blood pressure should be controlled before initiating SSNRI therapy.

Serotonin antagonist and reuptake inhibitors (SARIs)

- Mechanism of action
 - ⇒ Inhibition of serotonin reuptake → ↑ serotonin levels
 - ⇒ Antagonist of H₁- and α₁-receptors
- Drugs
 - ⇒ Trazodone
 - ⇒ Nefazodone
- Indications:
 - ⇒ major depressive disorder, especially in patients with insomnia
- Side effects
 - ⇒ Priapism
 - ⇒ Sedation (due to H₁ antagonism)
 - ⇒ Orthostatic hypotension
- Contraindications:

⇒ risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

Additional information

- ⇒ Mainly used as adjunct to other antidepressants for treatment of insomnia associated with depression
- ⇒ Off-label use: insomnia in patients without depression

Monoamine oxidase inhibitors (MAOIs)

- Mechanism
 - ⇒ inhibition of monoamine oxidase → ↓ breakdown of epinephrine, norepinephrine, and serotonin → ↑ levels of epinephrine, norepinephrine, and serotonin
- Drugs
 - ⇒ Tranylcypromine
 - ⇒ Phenelzine
 - ⇒ Selegiline
 - ⇒ Isocarboxazid
- Indications
 - ⇒ Major depressive disorder (third- or fourth-line therapy)
 - due to its potentially severe side effects, interaction with foods containing tyramine, and numerous drug interactions
 - ⇒ particularly effective for treating atypical symptoms of depression (↑ appetite and weight gain, ↑ sleep, leaden paralysis)
 - ⇒ Selegiline: Parkinson's disease (as an adjunct to carbidopa-levodopa)
 - For the treatment of depression, Selegiline is available as a transdermal patch
 - (oral form is only used for Parkinson's disease)
- Side effects
 - ⇒ Hypertensive crisis with ingestion of <u>foods containing tyramine</u> (e.g. aged cheeses, smoked/cured meats, alcoholic beverages, dried fruits)
 - ⇒ Serotonin svndrome
- Contraindications
 - ⇒ risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

<u>Tricyclic antidepressants (TCA)</u>

Dosulepin - avoid as dangerous in overdose

- Mechanism of action
 - ⇒ inhibition of serotonin and norepinephrine reuptake in synaptic cleft
 - → ↑ serotonin and norepinephrine levels
- Drugs

Tertiary amines	Secondary amines
Amitriptyline	Nortriptyline
Clomipramine	Desipramine
Doxepin	Protriptyline
Imipramine	
Trimipramine	

Indications

- ⇒ less commonly now for depression due to their side-effects and toxicity in overdose.
- ⇒ used widely in the treatment of neuropathic pain, where smaller doses are typically required.
- ⇒ prophylaxis of headache (both tension and migraine)
- ⇒ Major depressive disorder (third- or fourth-line therapy)
- ⇒ Neuropathy (diabetic neuropathy, post-herpetic neuralgia, etc.)
- ⇒ Chronic pain (including fibromyalgia)

Side effects

- ⇒ Orthostatic hypotension
- ⇒ Sedation and delirium
- ⇒ Anticholinergic symptoms
 - Cardiovascular symptoms:
 - wide QRS complex, tachycardia, arrhythmia (including ventricular fibrillation),
 - hypotension
 - CNS symptoms: drowsiness, confusion, hallucinations, sedation, coma, seizures
 - Gastrointestinal symptoms: intestinal ileus, constipation
 - Genitourinary symptoms: urinary retention
 - General:
 - Xerostomia (dry mouth)
 - blurred vision
 - mydriasis,
 - hyperthermia/dry skin

More sedative	Less sedative
Amitriptyline	Imipramine
Clomipramine	Lofepramine
Dosulepin	Nortriptyline
Trazodone (is technically a 'tricyclic-related)	. ,

Overdose

Lofepramine - the safest TCA in overdosage

- □ lofepramine has a lower incidence of toxicity in overdose
- amitriptyline and dosulepin (dothiepin) are considered the most dangerous in overdose
- ⇒ Clinical features: caused by anticholinergic effects
- ⇒ Management
 - Secure airways, oxygenation, monitoring, fluid resuscitation
 - ECG: cardiac arrhythmia (e.g., tachycardia, QRS prolongation)
 - Urine immunoassay: detection of TCA in the body
 - Activated carbon in first 2 hours after ingestion as soon as the airways are secured
 - Sodium bicarbonate for cardiac arrhythmia (QRS ≥ 100 ms or ventricula arrhythmias)
 - Benzodiazepines for seizures

Contraindications

- Risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
- ⇒ Tertiary amines are high-risk medications in the elderly population as they can cause confusion due to sedative and anticholinergic side effects.

Additional information

- ⇒ Rarely used as a first- or second-line antidepressant today due to extensive side effect profile and risk of lethal overdose (ingestion of a one-week supply can be fatal)
- ⇒ Physostigmine should not be given to patients with suspected TCA overdose because it can precipitate cardiac arrest
- Antimuscarinic side-effects are more common with imipramine than other types of tricyclic antidepressants.

Atypical antidepressants

Mirtazapine

- · Mechanism of action
 - \Rightarrow α_2 -adrenergic antagonist $\rightarrow \uparrow$ serotonin and norepinephrine release
 - \Rightarrow 5-HT₂ and 5-HT₃ receptor antagonist \rightarrow \uparrow effect of serotonin on free 5-HT₁ receptor \rightarrow likely responsible for antidepressant effects
 - ⇒ H₁ antagonist
- Indications
 - ⇒ major depressive disorder, especially in underweight and insomniac patients
- Side effects
 - ⇒ ↑ appetite and weight gain
 - ⇒ Sedation (due to H₁ antagonism)

Contraindications

⇒ risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use

Bupropion

- Mechanism of action
 - ⇒ not fully understood, but thought to increase dopamine and norepinephrine levels via reuptake inhibition
- Indications
 - Smoking cessation:
 - used in conjunction with counseling and nicotine replacement
 - ⇒ Major depressive disorder
 - ⇒ Depressive disorders with seasonal pattern
- Side effects
 - ⇒ Reduction of seizure threshold
 - ⇒ Tachycardia, palpitations, agitation
 - ⇒ Weight loss
 - ⇒ Neuropsychiatric symptoms (including depression, mania, psychosis, and paranoia)

Contraindications

- ⇒ Patients with ↑ risk for seizure (epilepsy, anorexia/bulimia, alcohol or benzodiazepine withdrawal, etc.)
- ⇒ Risk of serotonin syndrome if given concomitantly within 14 days of MAOIs, linezolid, or methylene blue use
- Additional information
 - ⇒ Bupropion has **no sexual side effects**, which makes it a viable alternative to SSRIs or SSNRIs for patients who experience sexual dysfunction.

Benzodiazepines

GABAA drugs

- · benzodiazipines increase the frequency of chloride channels
- barbiturates increase the duration of chloride channel opening

Frequently Bend - During Barbeque

...or...

Barbidurates increase duration & Frendodiazepines increase frequency

Benzodiazepines enhance the effect of GABA, the main inhibitory neurotransmitter

Action:

 Benzodiazepines (lorazepam, diazepam, chlordiazepoxide) enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

Indications

- Sedation
- Hypnotic
- Anxiolytic
- Anticonvulsant
- Muscle relaxant

Prescription

- Patients commonly develop a tolerance and dependance to benzodiazepines and care should therefore be exercised on prescribing these drugs.
- The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

Benzodiazepine withdrawal

- The BNF gives advice on how to withdraw a benzodiazepine:
- The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight.
- A suggested protocol for patients experiencing difficulty is given:
 - ⇒ Switch patients to the equivalent dose of diazepam
 - ⇒ Reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
 - ⇒ Time needed for withdrawal can vary from 1 month to 1 year or more

benzodiazepine withdrawal syndrome:

- If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome.
- This may occur up to 3 weeks after stopping a long-acting drug.

Features

- ⇒ Insomnia
- □ Irritability
- ⇒ Anxiety
- ⇒ Tremor
- ⇒ Tinnitus
- ⇒ Perspiration
- ⇒ Perceptual disturbances
- ⇒ Seizures

Flumazenil

- ⇒ Flumazenil, a benzodiazepine antagonist, is used to reverse the central sedative effects of benzodiazepines after anaesthetic and similar procedures
- ⇒ Flumazenil has a shorter half-life than that of diazepam and midazolam and there is a risk that patients may become re-sedated - in which case a repeat dose of flumazenil should be given

Which drug is more safer in overdose

- **Diazepam** has a long half-life, principally because of its active metabolites.
- Midazolam is short-acting but is only used intravenously.
- **Promethazine** is an antihistamine with a 12-hour half-life and may cause daytime sedation.
- Clomethiazole is less safe in overdose, has dependence potential and is only licensed for sedation in the elderly.
- Loprazolam is short-acting (half-life 6–12 hours).

Post-traumatic stress disorder

- Post-traumatic stress disorder (PTSD) can develop in people of any age following a traumatic event, for example a major disaster or childhood sexual abuse.
- It encompasses what became known as 'shell shock' following the first world war.
- One of the DSM-IV diagnostic criteria is that symptoms have been present for more than one month
- the onset of symptoms is usually delayed and it tends to run a prolonged course

Features

- re-experiencing: flashbacks, nightmares, repetitive and distressing intrusive images
- avoidance: avoiding people, situations or circumstances resembling or associated with the
 event
- hyperarousal: hypervigilance for threat, exaggerated startle response, sleep problems, irritability and difficulty concentrating
- emotional numbing lack of ability to experience feelings, feeling detached from other people
- depression
- · drug or alcohol misuse
- ander
- unexplained physical symptoms

Management

- following a traumatic event single-session interventions (often referred to as debriefing) are not recommended
- · watchful waiting may be used for mild symptoms lasting less than 4 weeks
- military personnel have access to treatment provided by the armed forces
- trauma-focused cognitive behavioural therapy (CBT) or eye movement desensitisation and reprocessing (EMDR) therapy may be used in more severe cases
- drug treatments for PTSD should not be used as a routine first-line treatment for adults. If drug treatment is used then paroxetine or mirtazapine are recommended

Post-concussion syndrome

Post-concussion syndrome is seen after even minor head trauma

Typical features include

- headache
- fatigue
- anxiety/depression
- dizziness

Grief reaction

It is normal for people to feel sadness and grief following the death of a loved one and this
does not necessarily need to be medicalised.

Grief stages: One of the most popular models of grief divides it into 5 stages.

- Denial: this may include a feeling of numbness and also pseudohallucinations of the deceased, both auditory and visual. Occasionally people may focus on physical objects that remind them of their loved one or even prepare meals for them
- Anger: this is commonly directed against other family members and medical professionals
- 3. Bargaining
- 4. Depression
- 5. Acceptance
- It should be noted that many patients will not go through all 5 stages.
- risk factors of Abnormal, or atypical, grief reactions
 - ⇒ more likely occur in women
 - ⇒ if the death is sudden and unexpected.
 - ⇒ problematic relationship before death
 - ⇒ if the patient has not much social support.
- Features of atypical grief reactions include:
 - ⇒ delayed grief: sometimes said to occur when more than 2 weeks passes before grieving begins
 - ⇒ prolonged grief: difficult to define. Normal grief reactions may take up to and beyond 12 months

Depression: screening and assessment

Screening

- The following two questions can be used to screen for depression
 - ⇒ 'During the last month, have you often been bothered by feeling down, depressed or hopeless?'
 - ⇒ 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'
 - ⇒ A 'yes' answer to either of the above should prompt a more in depth assessment.

Assessment

- There are many tools to assess the degree of depression including the Hospital Anxiety and Depression (HAD) scale and the Patient Health Questionnaire (PHQ-9).
- Hospital Anxiety and Depression (HAD) scale
 - ⇒ consists of 14 questions, 7 for anxiety and 7 for depression
 - ⇒ each item is scored from 0-3
 - produces a score out of 21 for both anxiety and depression
 - ⇒ severity: 0-7 normal, 8-10 borderline, 11+ case
 - ⇒ patients should be encouraged to answer the questions quickly

Patient Health Questionnaire (PHQ-9)

- ⇒ asks patients 'over the last 2 weeks, how often have you been bothered by any of the following problems?'
- ⇒ 9 items which can then be scored 0-3
- ⇒ includes items asking about thoughts of self-harm
- ⇒ depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe

NICE use the DSM-IV criteria to grade depression:

- 1. Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- 3. Significant weight loss or weight gain when not dieting or decrease or increase in appetite nearly every day
- 4. Insomnia or hypersomnia nearly every day
- 5. Psychomotor agitation or retardation nearly every day
- 6. Fatigue or loss of energy nearly every day
- 7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- 8. Diminished ability to think or concentrate, or indecisiveness nearly every day
- 9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Subthreshold depressive symptoms	Fewer than 5 symptoms
Mild depression	Few, if any, symptoms in excess of the 5 required to make the diagnosis, and symptoms result in only minor functional impairment
Moderate depression	Symptoms or functional impairment are between 'mild' and 'severe'
Severe depression	Most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms

 Psychotic symptoms such as delusions and hallucinations may occur in depression, and when they do, treatment with both an antidepressant and an antipsychotic is indicated.

Psychotic depression

- Psychotic depression: severe depression accompanied by psychotic features
- is uncommon but important due to high risk of suicide.
- The history of low mood predating the psychotic symptoms, also the fact that the
 auditory hallucinations and delusions are consistent with the depressive feelings of
 guilt, distinguish this from schizophrenia.

Depressive pseudodementia

- Short-term memory loss may occur in conjunction with depression (depressive pseudodementia) as well as being seen in dementia.
- The memory loss improves with treatment of the depression.

Features of depression

- Early morning wakening
- decreased appetite
- there may be life events that may have precipitated that illness
- weight loss,
- constipation.
- · loss of libido, impotence in men,
- fatigue and generalised body aches and pains.
- Retardation or agitation of behaviour may occur.

Early morning waking is a classic somatic symptom of depression and often develops earlier than general insomnia.

Suicide

Factors associated with risk of suicide following an episode of deliberate selfharm:

- · efforts to avoid discovery
- planning
- leaving a written note
- final acts such as sorting out finances
- violent method

These are in addition to standard risk factors for suicide

- male sex
- advancing age
- · unemployment or social isolation
- · divorced or widowed
- history of mental illness (depression, schizophrenia)
- history of deliberate self-harm
- · alcohol or drug misuse

Treatment

- In an Emergency Department the suicidal patient who declines to be admitted for observation and treatment should be managed as follows:
 - ⇒ Ensure that a member of staff stays with them at all times
 - ⇒ Call the duty psychiatrist
 - If they attempt to abscond before or during psychiatric assessment, the staff of the Emergency Department have a duty under Common Law to restrain the patient

A suicidal patient became agitated and insisted that she wanted to go home immediately. How should you proceed?

➡ Call the duty psychiatrist, and with other staff in the Emergency Department attempt to restrain her until they arrive

Depression in older people

- Older patients are less likely to complain of depressed mood
- Depression in elderly can depress cognitive function, hence cognition may be inaccurately depressed on measurement scales.
- In elderly patients, geriatric depression scale (GDS) is more appropriate than Becks
 depression scale, as the latter focuses heavily on somatic symptoms that frequently underscore depression in elderly patients.

Features

- physical complaints (e.g. hypochondriasis)
- agitation
- insomnia

Management

SSRIs are first line (adverse side-effect profile of TCAs more of an issue in the elderly)

Generalised anxiety disorder

SSRIs are the first-line pharmacological therapy for generalised anxiety disorder

Overview

- · GABA and serotonin levels are decreased
 - ⇒ **Low levels of γ-aminobutyric acid (GABA)** have been associated with anxiety disorders, including generalized anxiety disorder.
 - Benzodiazepines work as agonists on the GABA-A receptor, enhancing the effects of GABA in the central nervous system and thus relieving anxiety symptoms.
- Norepinephrine is increased.
- Anxiety is a common disorder that can present in multiple ways.
- NICE define the central feature as an 'excessive worry about a number of different events associated with heightened tension.'
- characterized by disproportionately excessive fear and anxiety about everyday things.

Diagnosis

- Always look for a potential physical cause when considering a psychiatric diagnosis. In anxiety disorders, important alternative causes include:
 - ⇒ hyperthyroidism,
 - ⇒ cardiac disease and
 - ⇒ medication-induced anxiety.
 - salbutamol.
 - theophylline.
 - corticosteroids.
 - antidepressants
 - caffeine
- Anxiety has to last longer than <u>six</u> months for a formal diagnosis of generalized anxiety disorder to be made.
- According to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders, a
 diagnosis of generalized anxiety disorder requires three symptoms out of six to be
 present:
 - 1. muscle tension,
 - 2. restlessness,
 - 3. irritability,
 - 4. fatigability,
 - 5. sleep disturbance, and
 - 6. difficulty concentrating.

Management:

NICE suggest a step-wise approach:

- step 1: education about GAD + active monitoring
- step 2: low intensity psychological interventions (individual non-facilitated self-help or individual guided self-help or psychoeducational groups)
- step 3: high intensity psychological interventions (cognitive behavioural therapy or applied relaxation) or drug treatment.
 - ⇒ Cognitive behavioral therapy is the psychotherapy of choice
- step 4: highly specialist input e.g. Multi agency teams

Drug treatment (step 3)

- NICE recommend pharmacological therapy if low-intensity psychological interventions have been unsuccessful.
- SSRI anti-depressants

- ⇒ the first-line pharmacological therapy
- ⇒ Sertraline is recommended first-line, and if contraindicated or not tolerated then any other SSRI or serotonin noradrenaline reuptake inhibitor (SNRI).
- ⇒ interestingly for patients under the age of 30 years NICE recommend you warn patients of the increased risk of suicidal thinking and self-harm.
- ⇒ Weekly follow-up is recommended for the first month
- buspirone
 - ⇒ is an azaperone, a chemically and pharmacologically distinct class of drugs.
 - ⇒ It is an effective treatment for generalised anxiety disorder, especially for people who are sensitive to cognitive impairment.
 - ⇒ action: (5-HT1A partial agonist)
 - ⇒ Side effects: **nasal congestion** commonly reported.
- beta-blockers
- benzodiazepines:
 - ⇒ use longer acting preparations e.g. diazepam, clonazepam

Hyperventilation syndrome (HVS):

- history of repeated admissions without a diagnosis and rapid recovery are all pointers towards hyperventilation syndrome (HVS).
- If a doctor encounters such presentation, the <u>Nijmegen questionnaire</u> can be used to test whether or not the patient has HVS.
 - ⇒ This questionnaire involves asking about 16 different symptoms such as chest pain and tingling fingers.
 - ⇒ Each one of these symptoms should be assigned a number from 0 to 4 according to how often it is felt.
 - ⇒ A score of more than 23 out of 64 is diagnostic of HVS.

Mood disorder

Cyclothymic disorder

- numerous periods of both depression (but not major depressive episodes) and hypomania for at least two years.
 - ⇒ The crucial feature of a major depressive disorder is a severe dysphoric mood and persistent loss of interest or pleasure in all usual activities.

Dysthymic disorder

• chronic depression with never a manic or hypomanic episode, for at least two years.

Bipolar I disorder

- severe alterations in mood (mania and depression) that are usually episodic and recurrent.
- Treatment
 - ⇒ Sodium valproate and carbamazepine are efficacious as first line treatment in the prophylaxis of manic and depressive episodes in bipolar I disorder. Lithium may be used if these anticonvulsants are ineffective.
 - ⇒ However, in the initial stages of manic episodes, the addition of drugs with potent sedative effects are often required, for example, clonazepam, lorazepam and haloperidol.
 - These drugs can be tapered and then discontinued as soon as the initial phase of the manic episode has subsided, and the effects of the anticonvulsants or lithium are seen clinically.

Bipolar II disorder

 characterised by one or more major depressive episodes, at least one hypomanic episode and NO manic episodes.

Cognitive behavioural therapy

Main points

- · useful in the management of depression and anxiety disorders
- usually consists of one to two hour sessions once per week
- · should be completed within 6 months
- patients usually get around 16-20 hours in total

Seasonal affective disorder (SAD)

Definition

depression which occurs predominately around the winter months.

Aetiology

• thought to be related to melatonin metabolism and changes during winter

Features

Symptoms of <u>hyperphagia</u>, <u>hypersomnia</u> and <u>weight gain</u> are more typical in SAD compared with matched non-seasonal controls.

Treatment

 <u>Bright light therapy</u> has been shown to be more effective than placebo for patients with SAD (exposing individuals to bright light for several hours a day)

Body dysmorphic disorder

Overview

- Body dysmorphic disorder (also known as dysmorphophobia) is a mental disorder where patients have a significantly distorted body image
- The pathology of the disorder is probably close to that of obsessive-compulsive disorder (OCD) and the symptoms respond to treatment with an selective serotonin-reuptake inhibitor (SSRI) but not a neuroleptic.

Features

 presents as a preoccupation with a presumed defect in appearance that may be an overvalued idea or may be delusional.

Diagnosis

- Diagnostic and Statistical Manual (DSM) IV criteria:
 - ⇒ Preoccupation with an imagine defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive
 - ⇒ The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
 - ⇒ The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in Anorexia Nervosa)

Post-partum mental health problems

Post-natal depression is seen in around 10% of women

Post-partum mental health problems range from the 'baby-blues' to puerperal psychosis.

The Edinburgh Postnatal Depression Scale may be used to screen for depression:

- 10-item questionnaire, with a maximum score of 30
- indicates how the mother has felt over the previous week
- score > 13 indicates a 'depressive illness of varying severity'
- sensitivity and specificity > 90%
- includes a question about self-harm

'Baby-blues'	Postnatal depression	Puerperal psychosis
Seen in around 60-70% of women Typically seen 3-7 days following birth and is more common in primips Mothers are characteristically anxious, tearful and irritable	Affects around 10% of women Most cases start within a month and typically peaks at 3 months Features are similar to depression seen in other circumstances	Affects approximately 0.2% of women Onset usually within the first 2-3 weeks following birth Features include severe swings in mood (similar to bipolar disorder) and disordered perception (e.g. auditory hallucinations)
Reassurance and support, the health visitor has a key role	As with the baby blues reassurance and support are important Cognitive behavioural therapy may be beneficial. Certain SSRIs such as sertraline and paroxetine* may be used if symptoms are severe** - whilst they are secreted in breast milk it is not thought to be harmful to the infant	Admission to hospital is usually required There is around a 20% risk of recurrence following future pregnancies

- paroxetine is recommended by SIGN because of the low milk/plasma ratio
- fluoxetine is best avoided due to a long half-life

Alcohol - problem drinking: management

- Alcohol is a common cause of hypoglycaemia and can be rapidly life-threatening if not recognised. Common initial symptoms are tachycardia and sweating.
- patients who abuse alcohol often are relatively hypotensive as they are often relatively dehydrated and are thin due to minimal food intake.

Nutritional support

 SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- · benzodiazepines for acute withdrawal
- **Disulfram**: promotes abstinence alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis
- acamprosate: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo-controlled trials
 - ⇒ is derived from taurine
 - ⇒ increases the γ-aminobutyric acid (GABA) level, which inhibits CNS activity
 - ⇒ has relatively few side-effects
- Naltrexone: reduces the pleasure that alcohol brings and craving when it is withdrawn, and can halve the relapse rates; however, it is associated with a number of adverse effects, including:
 - ⇒ nausea, vomiting, anxiety, nervousness, insomnia, lethargy, arthralgia, increased sweating and lacrimation, diarrhoea or constipation, increased thirst and liver and kidney dysfunction
 - particularly the GI symptoms recognised with naltrexone may discourage use in a patient with a previous history of IBS

Alcohol withdrawal

Alcohol withdrawal is the most common cause of paranoid psychosis with visual hallucination

Mechanism

- chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to benzodiazepines) and inhibits NMDA-type glutamate receptors
- alcohol withdrawal is thought to be lead to the opposite (decreased inhibitory GABA and increased NMDA glutamate transmission)

Features

- symptoms start at 6-12 hours
- peak incidence of seizures at 36 hours
- peak incidence of delirium tremens is at 72 hours
- if patients continue to abstain from alcohol they usually peak after about 72 hours and may last a week or more, but usually have resolved by 3 weeks.

	Minor Withdrawal	Alcoholic Hallucinosis	Withdrawal Seizure	Delirium Tremens
Time Since Last Drink	6-12 hours	12-24 hours	24-48	48-72 hours
Features	 Insomnia Tremor Anxiety Nausea Vomiting Headache Sweating Palpitations 	visual, auditory and tactile hallucinations.	generalised tonic-clonic seizures.	Autonomic instability (tachycardia, hypertension, and pyrexia), Disorientation Hallucinations Agitation

Withdrawal Seizure

- ⇒ Most patients will have single or few fits, and complete spontaneous disappearance is anticipated within 6-12 hours.
- ⇒ The presence of focal fits, more than six fits, a prolonged post-ictal phase or development of status epilepticus should suggest another diagnosis.
- ⇒ Around 30% of patients will go on to develop delirium tremens and prophylactic doses of diazepam or chlodiazepoxide are indicated.

Delirium tremens

- ⇒ the most severe form of alcohol withdrawal.
- ⇒ Onset is typically three to seven days after cessation of chronic alcohol ingestion.
- ⇒ characterised by
 - visual hallucinations,
 - autonomic instability (tachycardia, hypertension, pyrexia),
 - obtundation and confusion.
 - Sweating, tremors and agitation are also features.

Management

- benzodiazepines
 - ⇒ In hepatic impairment benzodiazepines with a shorter half-life (e.g. lorazepam and oxazepam) are preferred
- carbamazepine also effective in treatment of alcohol withdrawal
 - ⇒ at a starting dose of 800 mg per 24 hours
- phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures
 - ⇒ best avoided because of the risk of causing hypotension.
- Thiamine is also indicated in chronic alcoholism but is not as immediately important as diazepam.

Schizophrenia

Epidemiology

Risk of developing schizophrenia

- monozygotic twin has schizophrenia = 50%
- parent has schizophrenia = 10-15%
- sibling has schizophrenia = 10%
- no relatives with schizophrenia = 1%
- Schizophrenia is more common in social classes IV and V.
- Temporal lobe epilepsy
- Amphetamines may cause a state resembling hyperactive paranoid schizophrenia with hallucinations.

Schizophrenia: features

Schneider's first rank symptoms may be divided into auditory hallucinations, thought disorders, passivity phenomena and delusional perceptions:

Auditory hallucinations of a specific type:

- two or more voices discussing the patient in the third person
- thought echo
- voices commenting on the patient's behaviour

Thought disorder: occasionally referred to as thought alienation

- thought insertion
- thought withdrawal
- thought broadcasting

Passivity phenomena:

- bodily sensations being controlled by external influence
- actions/impulses/feelings experiences which are imposed on the individual or influenced by others

Delusional perceptions

 a two-stage process) where first a normal object is perceived then secondly there is a sudden intense delusional insight into the objects meaning for the patient e.g. 'The traffic light is green therefore I am the King'.

Other features of schizophrenia include

- · impaired insight
- incongruity/blunting of affect (inappropriate emotion for circumstances)
- · decreased speech
- neologisms: made-up words
- catatonia
- Concrete thinking where a patient cannot use abstraction to understand the meaning of a sentence. It is more common in schizophrenia.
- negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation)

Prognostic indicators

Factors associated with poor prognosis

- · strong family history
- · gradual onset
- low IQ
- · premorbid history of social withdrawal
- · lack of obvious precipitant

Schizophrenia: management

Key points

- first-line
 - ⇒ oral atypical antipsychotics are first-line
 - (amisulpride, olanzapine, quetiapine, risperidone and zotepine)
- if they fail to comply with this then, depot medication (either typical or atypical)
 - ⇒ The obvious benefit of depot medication is that it is administered at regular intervals (generally 2–4-weekly) by medical staff. Therefore, the patient does not have to remember to take it on a daily basis. Staff also know that the patient has definitely been receiving their medication.
 - ⇒ The drawbacks of depot medication are the discomfort of the injection and problems with the injection site, e.g. infection or abscess formation.
- cognitive behavioural therapy should be offered to all patients
- close attention should be paid to cardiovascular risk-factor modification due to the high rates of cardiovascular disease in schizophrenic patients (linked to antipsychotic medication and high smoking rates)

Electroconvulsive therapy (ECT)

Indications

- life-threatening depressive stupor, especially when a patient is refusing to eat and drink.
 - ⇒ This is used as it generally has a shorter onset of action than antidepressant medication, which takes 2–3 weeks to work.
- severe depression refractory to medication
- psychotic symptoms.

Contraindications

- Raised intracranial pressure
- Recent cerebrovascular accident
 - ⇒ Most guidelines state that a recent CVA (within 1 to 3 months) is a contraindication.

Side-effects

- Short-term side-effects
 - headache
 - nausea
 - > short term memory impairment
 - memory loss of events prior to ECT
 - cardiac arrhythmia
- Long-term side-effects
 - > some patients report impaired memory

Charles Bonnet syndrome (CBS)

Overview

- Charles Bonnet syndrome (CBS) is characterised by persistent or recurrent complex hallucinations (usually visual or auditory), occurring in clear consciousness.
- This is generally against a background of visual impairment (although visual impairment is not mandatory for a diagnosis).
- Insight is usually preserved.
- Well-formed complex visual hallucinations are thought to occur in 10-30 percent of individuals with severe visual impairment.
- Around a third find the hallucinations themselves an unpleasant or disturbing experience.
- This must occur in the absence of any other significant neuropsychiatric disturbance.

Epidemiology

- CBS is equally distributed between sexes and does not show any familial predisposition.
- Prevalence of CBS in visually impaired people is thought to be between 11 and 15 percent.

Risk factors include:

- Advanced age
- · Peripheral visual impairment
- · Social isolation
- Sensory deprivation
- Early cognitive impairment

Associated conditions

 The most common ophthalmological conditions associated with this syndrome are agerelated macular degeneration, followed by glaucoma and cataract.

Prognosis

• In a large study published in the British Journal of Ophthalmology, 88% had CBS for 2 years or more, resolving in only 25% at 9 years (thus it is not generally a transient experience).

Treatment

Reassurance is usually the best treatment

Delusions

Cotard syndrome

- Cotard syndrome is a rare mental disorder where the affected patient believes that they
 (or in some cases just a part of their body) is either dead or non-existent.
- This delusion is often difficult to treat and can result in significant problems due to patients stopping eating or drinking as they deem it not necessary.

Othello syndrome is a delusional belief that a patients partner is committing infidelity despite no evidence of this. It can often result in violence and controlling behaviour.

De Clerambault syndrome (otherwise known as erotomania), is where a **patient believes that a person of a higher social or professional standing is in love with them.** Often this presents with people who believe celebrities are in love with them.

Ekbom syndrome is also known as delusional parasitosis and is the **belief that they are infected with parasites or have 'bugs' under their skin.** This can vary from the classic psychosis symptoms in narcotic use where the user can 'see' bugs crawling under their skin or can be a patient who believes that they are infested with snakes.

Capgras delusion is the belief that friends or family members have been replaced by an identical looking imposter.

Personality disorders

1 Croonanty	onanty disorders		
Disorder	Features		
Antisocial	 Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest; Deception, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure; Impulsiveness or failure to plan ahead; Irritability and aggressiveness, as indicated by repeated physical fights or assaults; Reckless disregard for safety of self or others; Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations; Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another 		
Avoidant	 Avoidance of occupational activities which involve significant interpersonal contact due to fears of criticism, or rejection. Unwillingness to be involved unless certain of being liked Preoccupied with ideas that they are being criticised or rejected in social situations Restraint in intimate relationships due to the fear of being ridiculed Reluctance to take personal risks due to fears of embarrassment Views self as inept and inferior to others Social isolation accompanied by a craving for social contact 		

	 Impulsivity in potentially self damaging area (e.g. Spending, sex, substance abuse) Recurrent suicidal behaviour Affective instability Chronic feelings of emptiness Difficulty controlling temper Quasi psychotic thoughts Borderline - think nightmare girlfriend/boyfriend
	5 5 7
Dependent	 Difficulty making everyday decisions without excessive reassurance from others Need for others to assume responsibility for major areas of their life Difficulty in expressing disagreement with others due to fears of losing support Lack of initiative Unrealistic fears of being left to care for themselves Urgent search for another relationship as a source of care and support when a close relationship ends Extensive efforts to obtain support from others Unrealistic feelings that they cannot care for themselves
Histrionic	 Inappropriate sexual seductiveness Need to be the centre of attention Rapidly shifting and shallow expression of emotions Suggestibility Physical appearance used for attention seeking purposes Impressionistic speech lacking detail Self dramatization Relationships considered to be more intimate than they are
Narcissistic	Grandiose sense of self importance Preoccupation with fantasies of unlimited success, power, or beauty Sense of entitlement Taking advantage of others to achieve own needs Lack of empathy Excessive need for admiration Chronic envy Arrogant and haughty attitude Narcissistic - Steve Jobs's ex-wife thought he had this
Obsessive- compulsive	 Is occupied with details, rules, lists, order, organization, or agenda to the point that the key part of the activity is gone Demonstrates perfectionism that hampers with completing tasks Is extremely dedicated to work and efficiency to the elimination of spare time activities Is meticulous, scrupulous, and rigid about etiquettes of morality, ethics,

Disorder	Features		
	or values Is not capable of disposing worn out or insignificant things even when they have no sentimental meaning Is unwilling to pass on tasks or work with others except if they surrender to exactly their way of doing things Takes on a stingy spending style towards self and others; and shows stiffness and stubbornness Cognitive behavioural therapy (CBT) and exposure response prevention (ERP) is the best management		
Paranoid	 Hypersensitivity and an unforgiving attitude when insulted Unwarranted tendency to questions the loyalty of friends Reluctance to confide in others Preoccupation with conspirational beliefs and hidden meaning Unwarranted tendency to perceive attacks on their character 		
Schizoid	 Indifference to praise and criticism Preference for solitary activities Lack of interest in sexual interactions Lack of desire for companionship Emotional coldness Few interests Few friends or confidants other than family Schizoid - think Bruce Wayne/Batman from recent Christopher Nolan films		
Schizotypal	 Ideas of reference (differ from delusions in that some insight is retained) Odd beliefs and magical thinking Unusual perceptual disturbances Paranoid ideation and suspiciousness Odd, eccentric behaviour Lack of close friends other than family members Inappropriate affect Odd speech without being incoherent 		

Haptic hallucinations are hallucinations involving skin sensation in the absence of stimuli, and are common in situations of alcohol withdrawal and stimulant drug overdose. In this situation medication with a benzodiazepine is the most appropriate intervention.

Diagnosis

Borderline personality disorder is marked out by instability in moods, behaviour and relationships.

Diagnosis is confirmed by the presence of at least 5 of the following symptoms;

- 1. Extreme reactions including panic, depression, rage, or frantic actions to abandonment, whether real or perceived
- 2. A pattern of intense and stormy relationships with family, friends, and loved ones, often veering from extreme closeness and love to extreme dislike or anger

- Distorted and unstable self-image or sense of self, which can result in sudden changes in feelings, opinions, values, or plans and goals for the future (such as school or career choices).
- **4.** Impulsive and often dangerous behaviours, such as spending sprees, unsafe sex, substance abuse, reckless driving, and binge eating.
- Recurring suicidal behaviours or threats or self-harming behaviour, such as cutting Intense and highly changeable moods, with each episode lasting from a few hours to a few days.
- 6. Chronic feelings of emptiness and/or boredom.
- 7. Inappropriate, intense anger or problems controlling anger
- **8.** Having stress-related paranoid thoughts or severe dissociative symptoms, such as feeling cut off from oneself, observing oneself from outside the body, or losing touch with reality.

Panic disorder

Recurrent <u>sudden</u> attacks of intense anxiety or fear accompanied by physical symptoms (e.g. palpitations and a feeling of suffocation) without an obvious cause or trigger.

Definition

- recurrent attacks of <u>intense fear and discomfort</u>.
 - ⇒ recurrent spontaneous panic attacks without an obvious cause or trigger,

Pathophysiology

- Abnormal discharge from the <u>locus caeruleus</u> in the midbrain has been implicated in panic attacks. The locus caeruleus is the origin of most brain noradrenergic pathways.
- has a genetic component.

Features

- symptoms develop **suddenly** and usually peak in less than 10 minutes.
- psychiatric symptom:
 - ⇒ intense anxiety or fear, derealization or depersonalization, fear of losing control or "going crazy," and fear of dying.
- physical manifestations of intense fear. like:
 - palpitations, feeling of suffocation, diaphoresis, tremor, shortness of breath, chest pain, nausea, abdominal discomfort, dizziness, lightheadedness, paresthesias, crushing chest pain.

Diagnosis

- To diagnose panic disorder, symptoms must be present for <u>more</u> than one month after an attack.
- physical cause of the symptoms must be ruled out before establishing a diagnosis of panic disorder.

Differential diagnosis

 To distinguish it from a specific phobia, some of the attacks must occur without an environmental trigger.

Treatment:

- NICE recommend either cognitive behavioural therapy or drug treatment
- SSRIs are first-line.
 - ⇒ <u>Selective serotonin</u> reuptake inhibitors and **venlafaxine** (a serotonin norepinephrine reuptake inhibitor) are the first-line
- If SSRIs is contraindicated or no response after 12 weeks, then imipramine or clomipramine should be offered
- Benzodiazepines are often used in the acute management of panic disorder.

Acute confusional state

· also known as delirium or acute organic brain syndrome

Definition

- Sudden change in the mental state or sudden onset of behaviour that is out of character,
- Recent changes in behavior (within hours or days)

Risk factors

- Older people (≥ 65)
 - ⇒ affects up to 30% of elderly patients admitted to hospital.
- · cognitive impairment or dementia
- severe illness
 - ⇒ 20–30% of people on **medical wards** in hospital have delirium,
 - ⇒ 10% 50% of people who have surgery develop delirium
- Current hip fracture

Features - wide variety of presentations

- memory disturbances (loss of short term > long term)
- may be very agitated or withdrawn
- disorientation
- mood change
- visual hallucinations
- · disturbed sleep cycle
- poor attention

Diagnosis

- · By clinical assessment based on:
 - ⇒ Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria or
 - ⇒ short Confusion Assessment Method (short CAM) to confirm the diagnosis.
 - In critical care or in the recovery room after surgery, CAM-ICU should be used.

Differential diagnosis

- · Delirium vs dementia
 - ⇒ It can be difficult to distinguish between delirium and dementia because symptoms overlap, and some people may have both conditions.
 - Dementia tends to develop slowly, whereas delirium is characterised by sudden changes.
 - Dementia is generally a chronic, progressive disease for which there is no cure. Delirium is a potentially reversible condition if the causes are identified and they are treatable.
 - If clinical uncertainty exists over the diagnosis, initial management should be for delirium.

Treatment

- Non-pharmacological
 - ⇒ the first intervention → Interview the patient, take a history, assess mental state and try to reassure the patient.
 - Adults with delirium who are distressed or are a risk to themselves or others are not prescribed antipsychotic medication unless de-escalation techniques (Communication approaches) are ineffective or inappropriate.
 - ⇒ modification of environment
- Pharmacological
 - ⇒ treatment of underlying cause
 - ⇒ Sedation
 - When to use?
 - Sedation should only be used as a last resort and preferably only once the cause of the delirium has been established.
 - Which drug?
 - Haloperidol 0.5 mg orally: the 2006 Royal College of Physicians guidelines' recommended haloperidol 0.5 mg as the first-line sedative
 - Olanzapine: the 2010 NICE delirium guidelines advocate the use of haloperidol or olanzapine
 - Mirtazapine
 - enhances both noradrenergic and serotinergic transmission, would be a good antidepressant choice for an emaciated agitated elderly patients. (medical-masterclass.com 2017 mrcp part 2)
 - Mirtazapine blocks alpha-2, 5-HT2A and 5-HT3 receptors, thus increasing the amounts of both noradrenaline and serotonin in the synaptic gap. It also has a high affinity for H1 receptors, so it tends to cause weight gain and drowsiness, a good choice for a **thin** agitated patient.
 - For how long?
 - short-term (usually for 1 week or less) haloperidol or olanzapine
 - Contraindications
 - avoid antipsychotics in patients Parkinson's disease or dementia with Lewy bodies.

Hypnogogic and hypnopompic hallucinations

Definition

- Hypnogogic hallucinations:
 - occur at the transition from wakefulness to sleep
- hypnopompic hallucinations:
 - ⇒ occur at the transition from sleep to wakefulness.

Features

- Hallucinations can be visual, tactile, auditory or other sensory events, such as changes in location of body parts, and feelings of levitation or out of body experiences.
- Visual and auditory hallucinations are most common.

Treatment

- No specific treatment is required;
- some patients appear to benefit from tricyclic antidepressants, although they were not endorsed by a Cochrane review.

Third edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Ophthalmology

Updated

Acute angle closure glaucoma (AACG)

Definition: sudden and sharp **increase in intraocular pressure (IOP)** caused by an obstruction of aqueous outflow (most commonly as a result of an occlusion of the iridocorneal angle)

Pathophysiology: blockage of the trabecular meshwork $\rightarrow \downarrow$ drainage of aqueous humor from the eye $\rightarrow \uparrow$ IOP

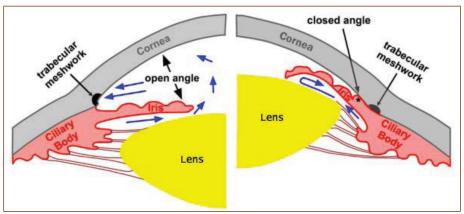


Image: mechanism of AACG

Risk factors

- hypermetropia (long-sightedness)
- · lens growth associated with age
- neovascular glaucoma (new blood vessels grow into the angle of the eye and block the
 aqueous outflow). Vascular endothelial growth factor (VEGF) is a growth factor protein that
 works by stimulating angiogenesis. Hence, inhibiting VEGF (e.g. Bevacizumab) can stop
 the progression of neovascularization.
- Drugs: pupillary dilatation by mydriatic drops, anticholinergics (e.g., atropine) and tricyclic antidepressants

Features

- Sudden onset of symptoms
- Unilaterally inflamed, reddened, and severely painful eye (hard on palpation)
- · Blurred vision and halos seen around light
- · Mid-dilated, irregular, unresponsive pupil
- Frontal headaches, vomiting, nausea
- Complications: rapid permanent vision loss due to ischemia and atrophy of the optic nerve symptoms worse with mydriasis (e.g. watching TV in a dark room)

Diagnosis

- Tonometry: → Elevated IOP (> 21 mm Hg)
- Gonioscopy: the gold-standard diagnostic test → Narrowing/closure of the iridocorneal angle.

Management

- · urgent referral to an ophthalmologist
- Acetazolamide intravenously, along with a topical beta-blocker and a topical alpha-agonist

- Reducing aqueous secretions with acetazolamide and inducing pupillary constriction with topical pilocarpine.
- Pilocarpine should not be the initial treatment as it is ineffective at pressures above 40 mmHq.
- Mannitol is typically reserved for refractory cases, not responding to the initial medical treatment.

Top Tips

Acute angle closure glaucoma is associated with hypermetropia, where as primary open-angle glaucoma is associated with myopia

Treatment of acute glaucoma - acetazolamide + pilocarpine

Do not use mydriatic drugs (e.g., atropine and epinephrine) during ophthalmologic examination in patients with acute angle-closure glaucoma! Moreover, do not cover the eye, since darkness induces mydriasis and worsens the condition

Primary open-angle glaucoma (POAG)

Epidemiology:

- The most common type of glaucoma. present in 2% of people older than 40 years.
- Second leading cause of blindness following age-related macular degeneration (AMD).

Pathophysiology

Secondary clogging of the trabecular meshwork or reduced drainage → gradual ↑ in IOP → vascular compression → ischemia to the optic nerve → progressive visual impairment.

Risk factors: age, family history, black patients, myopia, hypertension, diabetes mellitus **Features**:

- bilateral, progressive visual field loss (from peripheral to central) (Loss of nasal visual field) progressing to 'tunnel vision'
- Fundoscopy: cupping and pallor of optic disc

Management:

- Eye drops to lower intra-ocular pressure (IOP)
- Laser trabeculoplasty
 - ⇒ An alternative first-line treatment
 - ⇒ refractory to pharmacotherapy

Medication	Mode of action	Notes
Prostaglandin analogues (e.g. Latanoprost)	Increases uveoscleral outflow	Once daily administration Preferred first-line therapy. should be used first-line in patients with a history of asthma. Adverse effects: ⇒ brown pigmentation of the iris, ⇒ growth of eyelashes ⇒ Epithelial keratopathy ⇒ Systemic: paresthesia, hypokalemia, renal stones, acidosis, and aplastic anemia.
Beta-blockers (e.g. Timolol)	Reduces aqueous production	Should be avoided in asthmatics and patients with heart block
Sympathomimetics (e.g. brimonidine, an alpha2-adrenoceptor agonist)	Reduces aqueous production and increases outflow	Avoid if taking MAOI or tricyclic antidepressants Adverse effects include hyperaemia
Carbonic anhydrase inhibitors (e.g. acetazolamide)	Reduces aqueous production	Systemic absorption may cause sulphonamide-like reactions
Miotics (e.g. pilocarpine, a muscarinic receptor agonist)	Increases uveoscleral outflow	Adverse effects included a constricted pupil, headache and blurred vision

Age related macular degeneration (AMD)

Epidemiology

• The most common cause of blindness

Pathophysiology

progressive degenerative changes in the central part of the retina (macula) → visual impairment

Risk factors:

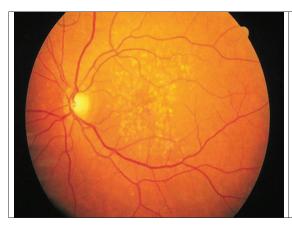
· Advanced age, smoking

Classification

	Dry AMD (nonexudative, atrophic)	Wet AMD (exudative , neovascular)
Prevalence	~ 90%	~ 10%
Pathophysiology	Deposition of drusen (yellow round spots) in the retinal pigment epithelium.	Choroidal neovascularization (between the retinal pigment epithelium and Bruch's membrane)
Onset	slow progressive visual impairment (usually over decades)	acute or insidious onset (over weeks to months)
Presentation	Bilateral	manifests in one eye
Fundoscopy	Drusen (a small, yellowish, granular, subretinal deposits that are age related).	Subretinal and intraretinal hemorrhage and/or exudate. if neovascularisation is present fluorescein angiography is performed
Treatment	Supportive: stop smoking Diet: high dose of beta-carotene, vitamins C and E, and zinc. Supplements should be avoided in smokers due to an increased risk of lung cancer	First-line: injection of VEGF inhibitors (ranibizumab, bevacizumab, pegaptanib) into the vitreous body.
Symptoms	Reduced visual acuity: 'blurred', 'distorted' vision, central vision is affected first (central scotomas)	

Differential diagnosis

Differential diagnosis of vision loss			
Condition	Clinical features	Fundoscopy	
Age related macular degeneration	 May be insidious (dry AMD) or rapid (wet AMD) onset Impairment of central vision only (vision loss is rare) 	Drusen Macula depigmentation	
Open-angle glaucoma	Insidious onsetPeripheral vision loss (tunnel vision)	Disc cupping with high intraocular pressure	
Central Vessel occlusion (retinal artery)	Acute or subacute onsetComplete vision loss	Swollen discRetinal haemorrhagesCotton wool spots	
Retinal detachment	Acute onsetPartial or complete vision loss (falling curtain)	Detached or floating retina	
Cataract	Insidious onsetBlurred, dim vision, and a glareAbsent or opacified red-reflex	Retina may not be visible (in advanced disease)	



The fundus shows small pale dots over the macular area typical of drusen.
This is macular degeneration and one of the commonest causes of blindness.



Top tips

Drusen = Dry macular degeneration

Macular degeneration - smoking is risk factor

Cataracts

Normal, clear lens



Lens clouded by cataract



A cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity

Definition

opacification of the lens

Causes

- Majority
 - ⇒ age related (Senile cataracts)
 - the most common cause
 - 17% of people older than 40 years
 - ❖ 50% of people older than 75 years
 - ⇒ UV light
- Systemic
 - ⇒ diabetes mellitus
 - ⇒ steroids
 - Inhaled steroids can cause cataracts
 - ⇒ infection (congenital rubella)
 - ⇒ metabolic:
 - diabetes
 - hypocalcaemia,
 - galactosaemia
 - but if the galactosaemia is treated, the cataract is reversible.
 - ⇒ myotonic dystrophy,
 - ⇒ Down's syndrome
- Ocular
 - ⇒ trauma
 - ⇒ uveitis
 - ⇒ high myopia
 - ⇒ topical steroids

Feature

- Symptoms
 - ⇒ painless, progressive, and slow vision loss
- Physical exam
 - ⇒ absent red reflex

Classification

- Nuclear sclerosis:
 - ⇒ the most common type of cataract,
 - ⇒ involves the central or 'nuclear' part of the lens.
 - ⇒ common in old age
 - ⇒ reduction of vision is the major symptom.

- ⇒ change lens refractive index.
 - often leads to an increase in refractive power of the lens causing nearsightedness (problems with distance vision).
- · Polar: localized, commonly inherited, lie in the visual axis
- Subcapsular:
 - ⇒ glare is the major symptom
 - Glare is difficulty seeing in the presence of bright light such as direct or reflected sunlight or artificial light such as car headlamps at night.
 - ⇒ due to steroid use, just deep to the lens capsule, in the visual axis
 - Posterior subcapsular cataracts are associated with:
 - retinitis pigmentosa
 - chronic steroid use.
 - ⇒ Anterior subcapsular cataracts are associated with:
 - idiopathic or
 - secondary to trauma and iotragenic causes.
- · Dot opacities
 - ⇒ common in normal lenses,
 - ⇒ also seen in:
 - diabetes
 - myotonic dystrophy

Diabetic retinopathy See endocrinology

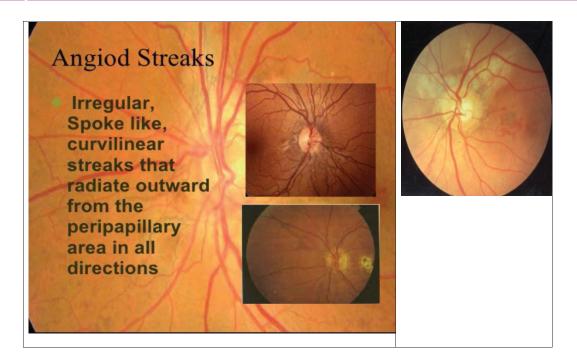
Angioid retinal streaks

 Angioid retinal streaks are seen on fundoscopy as irregular dark red streaks radiating from the optic nerve head. They are caused by degeneration, calcification and breaks in Bruch's membrane.

Causes

A useful mnemonic for angioid retinal streak is **SLAPPERS**:

- S Sickle-cell anaemia
- L Lead poisoning
- A Abetalipoproteinaemia/acromegaly
- P Paget's disease /phacomatoses (tuberous, sclerosis, neurofibromatosis, Sturge-Weber)
- P Pseudoxanthoma elasticum
- E Ehlers-Danlos syndrome
- R Raised calcium or phosphate
- S Short people (dwarfism).





Mydriasis

Causes of mydriasis (large pupil)

- third nerve palsy
- · Holmes-Adie pupil
- · traumatic iridoplegia
- phaeochromocytoma
- congenital
- Drug causes of mydriasis
 - ⇒ topical mydriatics: tropicamide, atropine
 - ⇒ sympathomimetic drugs: amphetamines, pseudoephedrine, amphetamines and cocaine,
 - ⇒ anticholinergic drugs: eg antihistamines, atropine and tricyclic antidepressants
 - ⇒ Poisons (atropine, CO, ethylene glycol).

Miosis

Causes of small pupils include:

- Horner's syndrome
- Old age
- · Pontine haemorrhage
- Argyll Robertson pupil
- Drugs, and
- Poisons (opiates, organophosphates).

Holmes-Adie pupil

Holmes ADIe = Dllated pupil, females, absent leg reflexes

Abnormally dilated pupil (mydriasis) which does not constrict in response to light, loss of deep tendon reflexes, and abnormalities of sweating.

Holmes-Adie pupil is a benign condition most commonly seen in women. It is one of the differentials of a dilated pupil.

Overview

- unilateral in 80% of cases
- dilated pupil (tonically dilated pupil)
- slowly reactive to accommodation but very poorly (if at all) to light
- once the pupil has constricted it remains small for an abnormally long time
- associated with absent ankle/knee reflexes and impaired sweating
 - The cause of the associated arreflexia is unknown.

Pathophysiology

- Viral or bacterial infection causes → damage to neurons in the ciliary ganglion, located in the posterior orbit, that provides parasympathetic control of eye constriction.
- damage to the dorsal root ganglia of the spinal cord → problems with autonomic control of the body.

Diagnosis

 testing with low dose (1/8%) pilocarpine may constrict the tonic pupil due to cholinergic denervation super-sensitivity. A normal pupil will not constrict with the dilute dose of pilocarpine.

Argyll-Robertson pupil

- the prostitute's pupil accommodates but doesn't react.
- Another mnemonic used for the Argyll-Robertson Pupil (ARP) is Accommodation Reflex Present (ARP) but Pupillary Reflex Absent (PRA)

Features

- · small, irregular pupils
- no response to light but there is a response to accommodate

Causes

- diabetes mellitus
- syphilis (neurosyphilis)

Anisocoria

- is a condition characterized by an unequal size of the eyes' pupils.
- Affecting 20% of the population,
- it can be an entirely harmless condition or a symptom of more serious medical problems
- The history of anisocoria, with headaches and diplopia should ring alarm bells, in that a life-threatening posterior communicating artery aneurysm/berry aneurysm needs to be excluded urgently.

Optic atrophy

- Optic atrophy is a descriptive term, it is the optic neuropathy that results in visual loss
- Usually bilateral and causes a gradual loss of vision.
- On fundoscopy optic atrophy is seen as pale, well demarcated disc.
- Causes may be acquired or congenital

Acquired causes

- multiple sclerosis
- papilloedema (longstanding)
- raised intraocular pressure (e.g. glaucoma, tumour)
- retinal damage (e.g. choroiditis, retinitis pigmentosa)
- ischaemia
- toxins: tobacco amblyopia, quinine, methanol, arsenic, lead
- nutritional: vitamin B1, B2, B6 and B12 deficiency

Congenital causes

- Friedreich's ataxia
- mitochondrial disorders e.g. Leber's optic atrophy
 - ⇒ usually affects young men.
 - ⇒ It causes sequential optic neuropathies in days to weeks.
 - ⇒ It is typically painless and severe.
 - ⇒ Visual acuity fails to improve.
 - ⇒ Mutations in the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 genes
 - These genes are contained in mitochondrial DNA.
 - ⇒ Specifically, more than 50% of males with a mutation and more than 85% of females with a mutation never experience vision loss or related medical problems.
- DIDMOAD the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)



This patient has **optic atrophy** as revealed by a particularly **pale disc**. Causes include:

- Glaucoma
- External compression of the optic nerves, for example, pituitary tumour, and
- Multiple sclerosis.

Optic neuritis

The patient sees nothing and the doctor sees nothing

- Optic neuritis is a broad term which can be used to describe inflammation, degeneration or demyelination of the optic nerve.
- Optic neuritis is very rare in people over the age of 50.
- It encompasses a number of conditions, including:
 - Papillitis (anterior optic neuritis) the intraocular portion of the nerve is affected, and the optic disc is swollen
 - It is important to note that the disc changes in papilloedema may closely resemble those of papillitis but visual acuity is markedly reduced in papillitis and not papilloedema.
 - ⇒ Retrobular neuritis the distal portion of the optic nerve is affected, and the disc is therefore not swollen
 - ⇒ Neuroretinitis optic disc and adjacent temporal retina are affected.

Causes

- multiple sclerosis
- diabetes
- syphilis

Features

- unilateral decrease in visual acuity over hours or days
 - ⇒ Visual loss typically occurs over days rather than hours. Sudden visual loss due to optic neuritis is very unusual.
 - Optic neuritis presents with a particular type of central visual loss a central scotoma.
- poor discrimination of colours, 'red desaturation' ie when red looks paler to one eye than the other -
- The retrobulbar neuritis seen with **ethambutol** may be unilateral or bilateral; as such unilateral symptoms do not preclude the diagnosis.

- pain worse on eye movement
- relative afferent pupillary defect during the 'swinging flashlight test'.
- central scotoma
- Most cases of optic neuritis are retrobulbar and hence there are no abnormalities on fundoscopy.
 - ⇒ the most likely finding on fundoscopy → Normal optic disc

Diagnosis

- MRI with gadolinium of the brain will likely show → enhancement of the optic nerve
- Abnormal visual evoked potentials (VEP)

Management

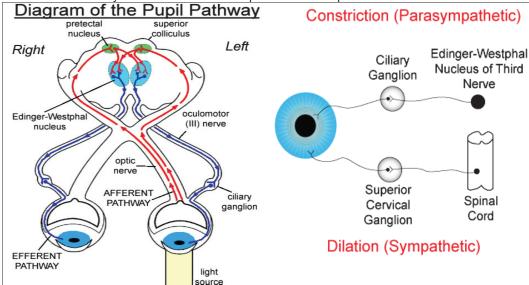
- · high-dose steroids
 - ⇒ Methylprednisolone pulse therapy is the standard treatment
 - slightly shortens the time of recovery but does not prevent neurodegeneration and persistent visual impairment.
- · recovery usually takes 4-6 weeks
- · erythropoietin may have neuroprotective effects in autoimmune optic neuritis

Prognosis

- MRI: if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%
- Retrobulbar neuritis has the same systemic implications as optic neuritis, in that an
 episode of optic or retrobulbar neuritis can contribute to a diagnosis of multiple sclerosis

Relative afferent pupillary defect

- Also known as the Marcus-Gunn pupil, a relative afferent pupillary defect is found by the 'swinging light test'.
- It is caused by a lesion anterior to the optic chiasm i.e. optic nerve or retina



Causes

- · retina: detachment
- · optic nerve: optic neuritis e.g. multiple sclerosis

Pathway of pupillary light reflex

- afferent: retina → optic nerve → lateral geniculate body → midbrain
- efferent: Edinger-Westphal nucleus (midbrain) → oculomotor nerve

Swinging flashlight test & Relative afferent pupillary defect RAPD (Marcus Gunn pupil)

- The Marcus Gunn pupil is a relative afferent pupillary defect indicating a decreased pupillary response to light in the affected eye
- In the swinging flashlight test, a light is alternately shone into the left and right eyes.
- A normal response would be equal constriction of both pupils, regardless of which eye the light is directed at. This indicates an intact direct and consensual pupillary light reflex.
- When the test is performed in an eye with an afferent pupillary defect, light directed in the
 affected eye will cause only mild constriction of both pupils (due to decreased response to
 light from the afferent defect), while light in the unaffected eye will cause a normal
 constriction of both pupils (due to an intact efferent path, and an intact consensual pupillary
 reflex). Thus, light shone in the affected eye will produce less pupillary constriction than
 light shone in the unaffected eye.
- A **positive** RAPD is due to retinal or optic nerve disease.

due to the consensual response of the pupillary light reflex, shining light in the unaffected eye will produce bilateral miosis.

- shining light in the affected eye will not produce miosis because the afferent limb of the pupillary light reflex pathway is damaged (eg: optic neuritis)
- ⇒ However, due to the bilateral projections of nerves from the Edinger-Westphal nucleus, light shined in the unaffected eye will produce bilateral miosis. This phenomenon is called a consensual response.

Herpes simplex keratitis

Herpes simplex keratitis most commonly presents with a dendritic corneal ulcer

Features

- red, painful eye
- photophobia
- epiphora
- · visual acuity may be decreased
- fluorescein staining may show an epithelial ulcer (dendritic corneal ulcer)

Management

- · immediate referral to an ophthalmologist
- · topical aciclovir

Herpes zoster ophthalmicus

- Herpes zoster ophthalmicus (HZO) describes the reactivation of the varicella zoster virus in the area supplied by the ophthalmic division of the trigeminal nerve.
- It accounts for around 10% of case of shingles.

Features

- vesicular rash around the eye, which may or may not involve the actual eye itself
- Hutchinson's sign: rash on the tip or side of the nose. Indicates nasociliary involvement and is a strong risk factor for ocular involvement

Management

- Oral antiviral treatment for 7-10 days, ideally started within 72 hours. Topical antiviral treatment is not given in HZO
- oral corticosteroids may reduce the duration of pain but do not reduce the incidence of postherpetic neuralgia
- ocular involvement requires urgent ophthalmology review

Complications

- · ocular: conjunctivitis, keratitis, episcleritis, anterior uveitis
- ptosis
- post-herpetic neuralgia

Blepharitis

- Blepharitis is inflammation of the eyelid margins.
- It may due to either meibomian gland dysfunction (common, posterior blepharitis) or seborrhoeic dermatitis/staphylococcal infection (less common, anterior blepharitis).
- Blepharitis is also more common in patients with rosacea
- The meibomian glands secrete oil on to the eye surface to prevent rapid evaporation of the tear film. Any problem affecting the meibomian glands (as in blepharitis) can hence cause drying of the eyes which in turns leads to irritation

Features

- · symptoms are usually bilateral
- grittiness and discomfort, particularly around the eyelid margins
- · eyes may be sticky in the morning
- · eyelid margins may be red. Swollen eyelids may be seen in staphylococcal blepharitis
- · styes and chalazions are more common in patients with blepharitis
- · secondary conjunctivitis may occur

Management

- softening of the lid margin using hot compresses twice a day
- mechanical removal of the debris from lid margins cotton wool buds dipped in a mixture of cooled boiled water and baby shampoo is often used*
 - ⇒ *an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled
- artificial tears may be given for symptom relief in people with dry eyes or an abnormal tear film

Keratitis

Definition

 Keratitis refers to inflammation of one or more of the three corneal layers, the most common of which is epithelial keratitis. This is characterised by dendritic ulcers. Rarer forms involve the stroma or endothelium.

Causes

- Pseudomonas aeruginosa is commonly associated with contact lens related infections.
- The management must also include advising the patient to discontinue wearing contact lenses and referral to a specialist ophthalmic unit.
- · Recurrence is common.

Keratitis overview		
	Characteristic features	Therapy
Bacterial keratitis (typically Staph. aureus Pseudomonas is seen in contact lens wearers.)	 ⇒ Most common form of keratitis ⇒ ↑ Risk with wearing contact lenses ⇒ Purulent discharge and/or hypopyon ⇒ Round corneal infiltrate or ulcer 	Topical broad-spectrum antibiotics (e.g., ciprofloxacin)
Herpes zoster keratitis	 → Corneal sensation → Punctate lesions on the corneal surface (early disease) → Vesicular eruption on forehead, bridge, and tip of the nose 	 Oral acyclovir, valacyclovir, or famciclovir Topical steroids
Herpes simplex keratitis	Dendritic or geographic corneal ulcer	Topical trifluridine or ganciclovir
Acanthamoeba keratitis	→ Risk with wearing contact lenses→ Corneal ring infiltrate	Topical antiseptic (e.g., chlorhexidine) with propamidine

Features

- Red eye: pain and erythema (**sharp ocular pain**)
- photophobia
- blurred vision (in many cases).
- Microbial keratitis, causing a white corneal infiltrate
- · foreign body, gritty sensation
- hypopyon may be seen

Dendritic ulcers

- caused by herpes simplex virus.
- Presentation is usually with pain, photophobia, blurred vision, conjunctivitis and chemosis.
- Steroid eye drops are contraindicated as they may induce massive amoeboid ulceration and blindness.
- treated with aciclovir eye drops, which should be continued for three days after the ulcer has healed.



Red eye

Red eye - glaucoma or uveitis?

- glaucoma: severe pain, haloes, 'semi-dilated' pupil
- · uveitis: small, fixed oval pupil, ciliary flush

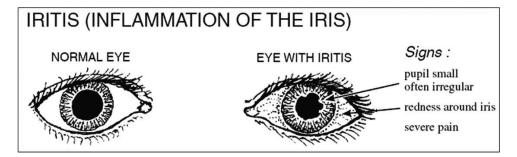
There are many possible causes of a red eye. It is important to be able to recognise the causes which require urgent referral to an ophthalmologist. Below is a brief summary of the key distinguishing **features**

Acute angle closure glaucoma

- severe pain (may be ocular or headache)
- · decreased visual acuity, patient sees haloes
- · semi-dilated pupil
- hazy cornea

Anterior uveitis

- Features
 - ⇒ acute onset
 - ⇒ pain
 - ⇒ blurred vision and photophobia
 - ⇒ small, fixed oval pupil, ciliary flush
 - ⇒ sign on ocular examination → Hypopyon
- Iritis is associated with conditions such as:
 - ⇒ Reiter's
 - ⇒ Behcet's
 - ⇒ Psoriatic arthropathy (about 20%)
 - ⇒ inflammatory bowel disease.
- Signs of anterior uveitis
 - ⇒ **Keratic precipitates**: (opaque aggregates of inflammatory cells deposited on the endothelium in anterior uveitis. They are typically located inferiorly.
 - ⇒ Cells +/- flare +/- fibrin in the anterior chamber
 - ⇒ Ciliary injection localised conjunctival injection (redness) around the limbus
 - ⇒ Posterior synechiae where part of the pupil margin becomes stuck to the lens
 - ⇒ Hypopyon (in severe anterior uveitis).



Scleritis

Definition

• inflammation that occurs throughout the entire thickness of the sclera,

Aetiology

- may be underlying autoimmune disease e.g. rheumatoid arthritis
 - ⇒ Around 50% of patients with scleritis have an underlying disease, of which the majority are connective tissue disorders.
 - ⇒ Rheumatoid arthritis is the most common.

Features

- severe pain (may be worse on movement) and tenderness
 - ⇒ **pain** in scleritis is more evident and severe than episcleritis.
 - ⇒ <u>Tenderness</u> to palpation of the globe can differentiate it from episcleritis. After asking the patient to look down with eyelids closed, the physician gently presses the globe. Patients with scleritis have tenderness on palpation, while those with episcleritis do not.
 - Unlike scleritis, patients with episcleritis do not complain of <u>blurred vision or photophobia</u>.
 - ⇒ Studies have shown that patients with RA-associated scleritis have <u>more</u> <u>widespread systemic disease</u> and a higher mortality rate than those episcleritis.
- 50% of cases are bilateral.
- Pain often radiates to the forehead, brow and jaw. This pain worsens with movement of the eye, and is classically worse at night.
- There is associated watering, photophobia and a gradual decrease in vision (sometimes with diplopia).
- Systemic symptoms such as fever, headache and vomiting can occur.
- On examination the globe is tender, and the sclera can have a bluish tinge.
- visual acuity is normal
- there is marked dilatation of the **deep and superficial** scleral vessels.
- Scleritis may cause thinning of the sclera (scleromalacia) and subsequent perforation.

Treatment

- Management ultimately depends on the underlying cause, but includes NSAIDs and prednisolone.
- The patient should be referred urgently to the ophthalmology clinic
- Application of topical phenylephrine 2.5% leads to blanching of episcleral vessels in episcleritis but not in scleritis.

Episcleritis

Scleritis is painful, episcleritis is not painful

- · Results in ocular irritation with nodules.
- acute in onset, with mild pain or discomfort / grittiness.
- can be unilateral or bilateral, with localised or diffuse red eye.
- There may be mild photophobia and watering. The lack of photophobia and discharge, and normal vision, makes episcleritis the most likely option

Ocular manifestation of rheumatoid arthritis (see rheumatology)

Conjunctivitis

- Purulent discharge if bacterial, clear discharge if viral
- Viral conjunctivitis
 - ⇒ causes redness, soreness and watering.
 - ⇒ In severe cases it can cause a keratitis which may affect vision.
 - ⇒ It is highly contagious so patients should be advised to practise strict hand hygiene, to avoid sharing towels and to take time off work.
 - ⇒ It is a self-limiting disease which may take several weeks to resolve.
 - ⇒ Patients are treated with topical lubricants and some ophthalmologists give topical chloramphenicol to protect against secondary bacterial infections.

Subconjunctival haemorrhage

- history of trauma or coughing bouts
- adverse effect of aspirin therapy (and other antiplatelets).
- It usually resolves over 10-14 days.
- If the haematoma is large it may be worth considering prophylactic antibiotic eyedrops.

Posterior uveitis

- Posterior uveitis describes inflammation of the choroid, which can involve the retinal vessels.
- presents with gradual visual loss and floaters, which is often bilateral.
- Discomfort and erythema are rare.
- Slit light examination can demonstrate inflammatory lesions on the retina or choroid, with inflammation of the retinal vessels and oedema of the optic nerve.

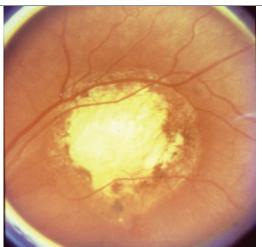
Retinitis

CMV Retinitis: causes hemorrhage at the edge of the area of retinal necrosis

- Retinitis is inflammation of the retina in the eye, which may lead to blindness.
- may be caused by several infectious agents, toxoplasmosis, cytomegalovirus and candida.
- Cytomegalovirus retinitis is the most common cause of vision loss in AIDS patients.

Toxocara retinitis

• In retinitis due to *Toxocara canis*, there is usually only a single, well demarcated lesion.



The slide shows the typical appearance of *Toxocara* retinitis with a lesion at the macula.

Retinitis pigmentosa

Retinitis pigmentosa - night blindness + funnel vision

Definition

• Retinitis pigmentosa is a <u>degenerative</u> disease involving retinal receptors and pigment cells.

Pathophysiology

- <u>degeneration of rod photoreceptor cells</u> in the retina → night blindness and low peripheral vision
 - ⇒ There are two types of photoreceptors, called rods and cones.
 - Rods are in the outer regions of the retina, and allow us to see in dim and dark light.
 - ❖ Died early → night blindness
 - Cones reside mostly in the central portion of the retina, and allow us to perceive fine visual detail and color.
 - Died in the late stages

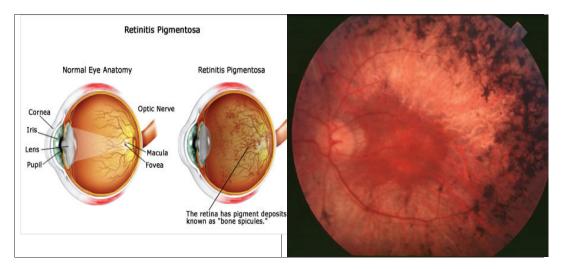
Features

- · night blindness is often the initial sign
- funnel vision (the preferred term for tunnel vision)
- fundoscopy:
 - ⇒ black bone spicule-shaped pigmentation in the peripheral retina.
 - ⇒ mottling of the retinal pigment epithelium

Associated diseases

- · Refsum disease:
 - ⇒ cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome

- · Alport's syndrome
- · mitochondrial myopathy
- drug-induced
 - ⇒ Thioridazine
 - (typical antipsychotic drug belonging to the phenothiazine group and was previously widely used in the treatment of schizophrenia and psychosis; withdrawn worldwide in 2005 because it caused severe cardiac arrhythmias,)
 - It is important to differentiate this from corneal deposits that may develop with the use of chlorpromazine.
 - ❖ Thioridazine → <u>retinal</u> deposits (<u>retinitis pigmentosa</u>).



Fundus showing changes secondary to retinitis pigmentosa

Sudden painless loss of vision

Causes	Notes
Central retinal vein occlusion	 Incidence increases with age More common than arterial occlusion Causes: glaucoma, polycythaemia, hypertension, DM Features: ⇒ afferent pupillary defect ⇒ On fundoscopy: widespread dot-and-blot and/or flame-shaped hemorrhages in all four retinal quadrants Cotton wool spots characterized by yellow-white deposits on the retina caused by swelling of retinal nerve fibers due to ischemia Severe macular edema and papilledema Fluorescein angiography: in order to differentiate ischemic from non-ischemic forms of retinal vein occlusion

Causes	Notes	
Branch retinal	Features:	
vein occlusion	⇒ Usually asymptomatic	
	⇒ No afferent pupillary defect	
Occident	⇒ the hemorrhages are found in a single zone.	
Central	Causes: thromboembolism (from atherosclerosis) or arteritis (e.g. temporal attention)	
Retinal artery occlusion	arteritis) • Features:	
occiusion		
	"descending curtain")	
	⇒ afferent pupillary defect,	
	⇒ history of amaurosis fugax, often describes as a 'black curtain'	
	descending over the vision.	
	⇒ On fundoscopy: 'cherry red' spot on a pale retina,	
	 Grayish-white (cloudy) discoloration of the entire retina 	
	Cherry-red spot at the fovea centralis	
Branch retinal	• Features:	
artery occlusion	⇒ Sudden onset of visual field defects (scotomas) in the affected eye	
Occiusion	 ⇒ No afferent pupillary defect, ⇒ On fundoscopy: Grayish-white discoloration of the retinal quadrant 	
	supplied by the affected vessel	
Retinal	Risk factors: Previous intraocular surgery (e.g., cataract surgery), posterior	
detachment	vitreous detachment	
	 Most commonly due to retinal tears → retinal fluid, which is formed by 	
	vitreous degeneration, seeps into the subretinal space $ ightarrow$ retinal detachment	
	Features:	
	⇒ Prodromal symptoms: result from posterior vitreous detachment	
	(floaters, flashes of light (photopsia)	
	⇒ Localized retinal detachment: scotoma (visual field defect): Dense shadow that starts peripherally progresses towards the central vision	
	⇒ Straight lines appear curved	
	⇒ Extensive retinal detachment and/or macular involvement: Central	
	visual loss (often described by patients as a curtain descending over	
	their field of vision)	
	⇒ Fundoscopy: A freshly detached retina has a grey color instead of the	
\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \		
1111111111		
naemorrnage		
	⇒ Fundoscopy: inability to visualise the retina	
Vitreous haemorrhage	normal pink color and may appear crinkled. A retinal tear may be visible • Causes : bleeding disorders, DM → Proliferative retinopathy → rupture fragile neovascular vessels (most common cause) • Features: □ Large bleeds cause sudden visual loss □ Moderate bleeds may be described as numerous dark spots □ Small bleeds may cause floaters	

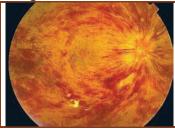
Amaurosis fugax

- Definition: sudden, painless loss of vision that lasts for seconds to minutes and is followed by spontaneous recovery (mostly unilateral)
- Cause: retinal ischemia following transient occlusion of the central retinal artery by microemboli
- Complications: Transient ischemic attacks (TIA)

Posterior vitreous detachment

- Occur in up to 50-75% of the population over 65 years
- Features:
 - ⇒ Flashes of light (photopsia) in the peripheral field of vision
 - ⇒ Floaters, often on the temporal side of the central vision
- Complications: Retinal tears/holes, retinal detachment, Vitreous hemorrhage

Images



Central vein occlusion:

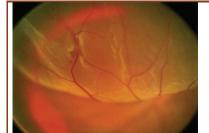
Flame-shaped hemorrhage is visible in all four retinal quadrants.



Central retinal artery occlusion:

Narrow retinal arteries and a pale retina with early signs of nerve fiber layer edema are visible.

The fovea centralis appears red (cherry-red spot; due to the transparency of the well-vascularized choroid, as no nerve fibers are present in the fovea avascular zone. Therefore, there is no edema.



Retinal detachment:

The retina is visible as a yellow-grey, bullous elevation in the upper part of the image.

- Green overlay: detached retina
- Red overlay: tear



Fundus Photograph of Vitreous Haemorrhage

Central retinal vein occlusion - sudden painless loss of vision, severe retinal haemorrhages on fundoscopy

Flashes and floaters - vitreous/retinal detachment

An elderly patient with acute visual loss has giant cell arteritis until proved otherwise

The history of diabetes, complete loss of vision in the affected eye and inability to visualise the retina point towards a diagnosis of vitreous haemorrhage.

Nasal branch retinal vein occlusion \rightarrow sudden <u>blurring</u> (not total visual loss) of the temporal field in the affected eye.

Of all types of retinal vessel occlusion, ischemic Central Retinal Vein Occlusion is most commonly associated with neovascularization.

Tunnel vision

Tunnel vision (also known as **Kalnienk vision**) is the loss of peripheral vision with retention of central vision, resulting in a constricted circular tunnel-like field of vision. **Causes**

- papilloedema
- glaucoma
- retinitis pigmentosa
- choroidoretinitis
- · optic atrophy secondary to tabes dorsalis
- hysteria

Ectopia lentis

Ectopia lentis/subluxation of the lens is associated with:

- Ehlers-Danlos syndrome
- · Marfan's syndrome
- Weill-Marchesani syndrome (short stature, skeletal abnormalities and ectopia lentis), and
- · Refsum's disease.

Fundoscopic features in eye infections

- Cytomegalovirus (CMV) retinitis
 - ⇒ secondary to human immunodeficiency virus (HIV)
 - ⇒ Fundoscopy of the left eye revealed an extensive 'brushfire-like' lesion in the major superior temporal arcade with a large patch of white fluffy lesion mixed with extensive retinal haemorrhages.
- Ocular histoplasmosis and syphilitic choroiditis would give a fundus picture of multiple whitish lesions.
- Syphilitic neuroretinitis would normally give a picture of a macular star exudation.
- Tuberculous periphlebitis gives a picture of perivenous sheathing and minimal retinal haemorrhages.

Eye signs in Systemic diseases

- <u>Lisch nodules</u> of the iris are golden nodules occurring bilaterally in the teenage
 years onwards in Neurofibromatosis type 1 (NF-1). Axillary freckles appear at 10 years
 of age, while cafe au lait spots increase in size and number throughout childhood.
- Brushfield spots of the iris are found in people with Down syndrome.
- Kayser-Fleischer rings are due to copper deposition in Descemet's membrane of the cornea.
- <u>Band keratopathy</u> is caused by calcium deposition in Bowman's layer of the cornea.
 Patients who present with band keratopathy should have a serum calcium and phosphate level
- Ectopia lentis with aortic regurgitation → Marfan syndrome (Lens dislocation (classically upwards)).
 Inferior dislocated lens → consistent with a diagnosis of homocytinstinuria.
- Roth's spots haemorrhages in the retina → associated with subacute bacterial endocarditis, also, seen in leukaemia.
- 'black sunburst' a chorioretinal scar, which is one of the commoner retinal manifestations of Sickle cell disease (SCD) and pathognomonic.

Hyphaema

Overview

- Occurs when bleeding from iris vessels fills the anterior chamber with blood and if there is enough blood
- the main risk in the acute stage is of raised intraocular pressure (IOP).
- It is usually caused by trauma often small objects (champagne corks, squash balls) hitting the eye.

Treatment

- Strict rest is vital if a hyphaema is present, as there is an increased risk of a second bleed in the initial period.
- Intravenous carbonic anhydrase inhibitors is the most appropriate treatment
- Aspiration may be required to prevent loss of vision.
- avoid drops that dilate the pupil (such as anticholinergics) the iris remains stable and a second bleed is therefore less likely.



The slide shows hyphaema: blood in the anterior chamber.

Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Pharmacology

Updated

Basic pharmacology

Pharmacokinetics: metabolism

Drug metabolism

- · phase I: oxidation, reduction, hydrolysis
- · phase II: conjugation
- Drug metabolism usually involves two types of biochemical reactions phase I and phase II reactions.
- . The majority of phase I and phase II reactions take place in the liver
- Phase I reactions: oxidation, reduction, hydrolysis.
 - ⇒ Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase.
 - ⇒ Products of phase I reactions are typically more active and potentially toxic
- Phase II reactions: conjugation.
 - ⇒ Products are typically inactive and excreted in urine or bile.
 - ⇒ Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved

In the elderly population, phase I reactions will usually become impaired before phase II reactions.

Drug absorption

- Diffusion.
 - ⇒ **Most drug absorption** in the gastrointestinal tract occurs **by diffusion**.
 - ⇒ For diffusion to occur:
 - the drug must be dissolved so that individual drug molecules come into contact with the gut epithelium,
 - the drug must be lipid soluble so that it can cross the cell membrane.
 - Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly.
 - Drugs that are not ionized are lipid soluble and most likely to be well absorbed from the gastrointestinal tract.
 - The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily.
- Theoretically, weakly acidic drugs (eg, <u>aspirin</u>) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (eg, <u>quinidine</u>). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable

Lipid soluble drug vs lipid insoluble drug

lipid soluble drug	lipid insoluble drug
have good gastrointestinal absorption	have poor gastrointestinal absorption
can be given orally	may need to be given parenterally
will be widely distributed in the body (large volume of distribution)	has limited distribution (may not cross blood- brain barrier or placenta and less likely to be stored in fat tissue)
usually requires metabolism before elimination (to decrease lipid solubility)	may be eliminated without metabolism
often have a long plasma half-life (prolonged by 'reservoir' of drug in tissues and by requirement for metabolism).	often have a short plasma half-life as elimination does not require metabolism.

MRCPUK-part-1-Sep 2017: What is the mechanism that make salmeterol acts as a LABA?

→ Its long duration results from its high lipid solubility

Lipophilic, Hydrophilic and Amphiphilic

	Chemical nature	Clinical significance	Example
Lipophilic	Predominantly nonpolar compounds	can easily diffuse across the lipid bilayer of the cell membrane. ⇔ can be administered topically ⇔ can across the bloodbrain barrier Metabolised in the liver and then excreted through the bile duct	Scopolamine (hydroscine) ⇒ Tertiary amine ∪sed to treat motion sickness
Hydrophilic	Predominantly polar compounds	 can only cross the lipid bilayer via facilitated transport Smaller hydrophilic molecules can diffuse along a concentration gradient through pores in the membrane eliminated by the kidneys 	Butylscopolamine (hyoscine butylbromide)
Amphiphilic	Both lipophilic and hydrophilic		Local anesthetics, e.g., lidocaine

Drug metabolism in patients with advanced liver disease

- Plasma proteins fall in liver disease and may negatively affect drug distribution
- Both intrahepatic and extrahepatic cholestasis may affect the **metabolism** of drugs that are actively secreted into bile, eg ciprofloxacin
- Conjugation reactions are affected to a lesser extent by advanced liver disease and only occur in very late stage disease

Pharmacokinetics in chronic renal failure

- Renal failure disturbs virtually every kinetic parameter including:
 - ⇒ gastric absorption
 - ⇒ hepatic metabolism of some drugs
 - ⇒ protein binding
 - ⇒ volume of distribution

 The bioavailability of an intravenously administered drug is 100% and does not change in renal failure

What is the reason for phenytoin toxicity in patient with chronic renal failure?

- → Decreased protein binding of phenytoin
 - In CRF, drugs lose some of their affinity for protein binding →↑↑ availability of free drug at any given dose → toxicity
 - Because laboratory assays for phenytoin usually measure total drug concentration, this
 give a false re-assurance (drug level may be within therapeutic range)
 - In CRF dose reduction of phenytoin is therefore required
 - Other drugs may cause same problem → sodium valporate and warfarin

First-pass metabolism

- This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to <u>hepatic</u> metabolism.
 - ⇒ As a consequence much larger doses are need orally than if given by other routes.

. This effect is seen in many drugs, including:

⇒ Aspirin	⇒ verapamil
⇒ isosorbide dinitrate	⇒ isoprenaline
⇒ glyceryl trinitrate	⇒ testosterone
⇒ lignocaine	⇒ hydrocortisone
⇒ propranolol	

 Drugs with high first-pass metabolism should be used with caution in liver disease, since poor hepatic function may lead to their accumulation because of increased bioavailability

What is the reason for a different dose of sublingual glyceryl trinitrate (GTN) and oral isosorbide mononitrate?

⇒ First-pass metabolism

Drug kinetics (first order + zero order kinetics)

- In drugs which have saturation kinetics → initially Small doses of the drug lead to a linear increase in serum drug concentration(follow a linear line) → first order kinetics
- Then their metabolism slows down leading to a plateau of the line, for example due to
 enzyme depletion. Small doses in the drug then lead to large increases in plasma
 concentration → zero order kinetics.
- Types of drug kinetics
 - ⇒ Zero order kinetics:
 - The rate of metabolism and/or elimination remains constant and is independent of the plasma concentration of a drug at steady state (Cp decreases linearly over time)
 - Zero-order is a capacity-limited elimination.
 - Examples include
 - ethanol
 - phenytoin
 - aspirin (at high concentrations)
 - ⇒ First order kinetics:
 - The rate of metabolism and/or elimination is directly proportional to the plasma concentration of the drug (Cp decreases exponentially over time)
 - First-order is a flow-dependent elimination.
 - Applies to most drugs

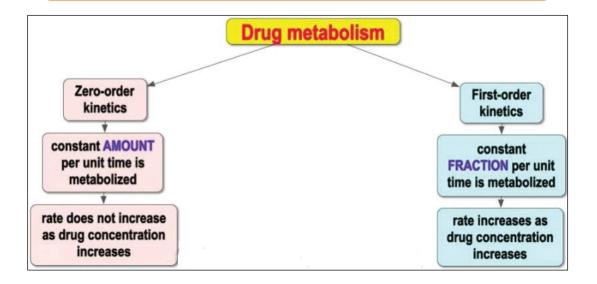
Zero-order kinetics

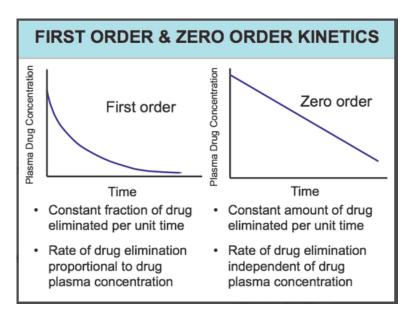
Zero-order (saturation) kinetics

- phenytoin
- alcohol
- Zero-order kinetics describes: metabolic pathways becoming saturated resulting in constant <u>amount</u> of drug being eliminated per unit time (metabolism which is independent of the concentration of the reactant).
- This explains why people may fail a breathalyser test in the morning if they have been drinking the night before
- Drugs following zero order kinetics continue to be metabolised at a steady rate, independent of the concentration of the substrate.
- . The plot of metabolism against time is linear.

Drugs exhibiting zero-order kinetics

- Phenytoin
- Salicylates (e.g. high-dose aspirin)
- Heparin
- Ethanol





Acetylator status

- 50% of the UK population are deficient in hepatic N-acetyltransferase
- Greater than 60% of Japanese are recognised to be fast acetylators
- Approximately 50% of black and Caucasian people are 'slow acetylators' and the rest are 'rapid acetylators'.
- The majority of Eskimos and Orientals are 'rapid acetylators'.
- Slow acetylation → ↑↑drug concentrations → ↑↑toxicity from drugs adverse effects.
- Fast acetylation:
 - ⇒ ↓↓response to the drug effect
 - ⇒ ↑↑ blood levels of the toxic metabolite

Drugs affected by acetylator status (slow acetylators → increased unwanted effects)

- 1. isoniazid
 - ⇒ Slow acetylation →↑↑ drug concentrations → (peripheral neuropathy and toxic hepatitis)

 hepatitis

 → ↑↑ drug concentrations → (peripheral neuropathy and toxic hepatitis)

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 → ↑↑ drug concentrations → (peripheral neuropathy and toxic hepatitis)

 → ↑↑ drug concentrations → (periph
- 2. hydralazine → drug-induced lupus
- 3. dapsone → haemolysis and neuropathy but not fibrosis
- 4. sulfasalazine → haemolysis
- 5. procainamide

Half-life

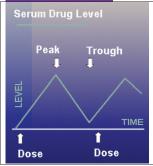
 $\uparrow\uparrow$ lipid solubility \Rightarrow $\uparrow\uparrow$ tissue binding of the drug $\Rightarrow\downarrow\downarrow$ renal and hepatic clearance rate $\Rightarrow\uparrow\uparrow$ half life

- The half-life is the time taken for the concentration of a drug to reduce by 50%
- Plasma half-life is the most important pharmacokinetic factor in determining the appropriate timing between doses
- The half-lives are related to:
 - 1. lipid solubility (amiodarone, fluoxetine and diazepam are very lipid-soluble)
 - 2. the rate of drug clearance

- Steady state: Drug concentration stays constant because the rate of drug elimination equals the rate of drug administration
- It takes 1 half-life to reach 50% of the steady-state level, 2 half-lives to reach 25%, 3 half-lives to reach 12.5%, and 4 half-lives to reach 6.25%.
- Complete steady-state attainment takes 4–5 half-lives for drugs infused at a constant rate;
 90% of steady-state level is reached after 3.3 half-lives
- Amiodarone the longest half-life = 25 days, fluoxetine 53 h; diazepam 43 h; gentamicin
 2-3 h; and bumetanide 0.8 h

After 4 half-lives, more than 90% of the drug is eliminated

Trough level



- The <u>lowest concentration</u> reached by a drug <u>before the next</u> dose is administered, often used in therapeutic drug monitoring.
- <u>Half-life</u> is the major determinant of trough concentration.
- A peak is the highest level of a medication in the blood, while a trough level indicates the lowest concentration.

Affinity & efficacy

Drug affinity

a measure of the tendency of a drug to bind to its receptor

Drug efficacy

 the maximum degree to which a drug activates receptors after binding and triggers a cell response

Potency

- The potency of a drug is measured as the concentration required to produce a pharmacological response of a specified intensity.
- Not related to efficacy (drugs with a high potency can have a low efficacy) but dependent on affinity

Therapeutic index

- a measurement of the safety of a drug
- The greater the therapeutic index, the safer the drug
- Drugs with a narrow therapeutic index require monitoring (e.g., lithium, theophylline, warfarin, digoxin, and antiepileptic drugs).

Dosage intervals

Loading dose

Why is a loading dose used in amiodarone? Because Amiodarone is widely bound in body tissues

- **Definition:** the amount of an initial dose of a certain drug needed to reach a target plasma concentration
- Formula: loading dose = (Cp x Vd) / F
 - ⇒ Cp = target peak plasma concentration at steady state (mg/L or units/L)
 - ⇒ Vd = volume of distribution (L/kg)
 - ⇒ F = bioavailability
- In patients with renal and/or liver dysfunction, loading dose (which does not depend on drug clearance) and time to steady-state are usually unaffected.
- Tissue-binding sites must be 'filled up' by a loading dose before a therapeutic plasma concentration can be achieved.
- Metabolism/elimination/clearance rates and plasma half-life determine the time taken to achieve a steady-state plasma concentration and the level of that steady-state concentration when a steady dosing regimen is established.
- The loading dose is mainly dependent on the volume of distribution of a drug but in patient with moderate renal failure it depends on renal clearance.
- Volume of distribution becomes important particularly when body weight is 40 kg or less.
- What is the main factor that determines the choice of loading dose of <u>digoxin</u> in patient with high creatinine?
 - → Renal clearance
 - Digoxin is cleared by the kidneys, so the maintenance dose would require adjustment in renal failure.
 - In digoxin both the initial loading dose and the maintenance dose must be reduced in patients with underlying renal disease.
- Most useful for drugs which have a long half-life such as:
 - ⇒ Amiodarone
 - ⇒ Digoxin
 - ⇒ Teicoplanin
 - antibiotic → inhibit bacterial cell wall synthesis.
 - spectrum of activity similar to vancomycin → against Gram-positive bacteria including Staphylococci and Clostridium spp. Oral teicoplanin is effective in the treatment of pseudomembranous colitis
 - ⇒ Voriconazole
 - ⇒ Procainamide
 - ⇒ Fulvestrant (selective estrogen receptor degrader (SERD). used to treat hormone receptor (HR)-positive metastatic breast cancer)

Renal or liver conditions lower the maintenance dose without affecting the loading dose.

The main factor influencing the time to steady-state is Half-life (t½), not dose or administration frequency.

Maintenance dose

- **Definition:** The amount of a certain drug needed to achieve a steady target plasma concentration.
- Formula: maintenance dose = (Cp x Cl * τ) / F
 - ⇒ Cp = target plasma concentration at steady state (mg/L)
 - ⇒ CI = clearance (L/h)
 - \Rightarrow τ = dosing interval (hours)
 - ⇒ F = bioavailability
- In patients with renal and/or liver dysfunction, maintenance dose is decreased (because of impaired drug clearance) and time to steady-state is unchanged (time to steady state depends on t½).

Loading dose vs maintenance dose:

- Loading doses usually do not need to be adjusted in patients with chronic kidney disease, but maintenance doses should be adjusted by: dose reduction, lengthening the dosing interval, or both.
- in renal or liver disease, dosage of the same drug when given as maintenance dose is decreased and when it is given as loading dose is usually unchanged.

Clinical trial: phases

Clinical trials are commonly classified into 4 phases;

Phase	Goal	Notes
I	Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies	Conducted on healthy volunteers
II	Assess efficacy + dosage	Involves small number of patients affected by particular disease May be subdivided into: Ila - assesses optimal dosing Ilb - assesses efficacy
III	Assess effectiveness	Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments
IV	Postmarketing surveillance	Monitors for long-term effectiveness and side- effects

How many patients would need to be recruited to detect one adverse event?

- Roughly speaking, to detect one adverse event in a clinical trial you would need to enrol three times as many patients as the expected event frequency
- So If the frequency expected was 1 in 10 000, then you would need to recruit 30 000
 patients

Prodrugs

Definition

• A drug that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent; (a precursor of a drug).

Prodrug	Active form	Note
Levodopa	Dopamine	converted by dopa decarboxylase to
		dopamine in the brain (in the striatum).
Enalapril	Enalaprilat	
S-methyldopa	Alpha methylnorepinephrine	It is converted to α -methylnorepinephrine by dopamine betahydroxylase \rightarrow activation of α_2 adrenergic receptors in the brainstem \rightarrow \downarrow sympathetic output \rightarrow \downarrow BP.
Loratadine	desloratadine	non-sedating antihistamine
Terfenadine	fexofenadine	 non-sedating antihistamine Terfenadine, withdrawn from the market because of serious side effect. fexofenadine, is safe, does not carry the same risks as the parent compound.
salicin	salicylic acid	salicin is a β-D-glucopyranoside that is cleaved by esterases to release salicylic acid.
codeine and morphine	(morphine- glucuronides)	codeine and morphine is enzymatically activated to form sugar derivatives (morphine-glucuronides) that are more active than the parent compound
Mercaptopurine	Methymercaptopurine ribonucleotide	
Fluouracil	Fluororidine monophosphate	
Cyclophosphamide	Aldophosphamide, Phosphormide mustard	
Sulfasalazine	5-Aminosalicyclic acid	
Becampicillin	Ampicillin	
Prednisone	Prednisolone	
Proguanil	Proguanil triazine	Antimalarial is an inhibitor of dihydrofolate reductase
Hydrazide MAO inhibitors	Hydrazine derivatives	
Dipivefrine	Epinephrine	used to treat open-angle glaucoma

P450 enzyme system

3 "O" antibiotics inhibitOrs → isOniazid, ciprOfloxacine, erythrOmycin

1 "C " antibiotic induCer → rifampiCine

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inhibitors of the P450 system include

Isoniazid inhibits the P450 system

- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- · cimetidine, omeprazole
- amiodarone
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- sulphonamides
- Disulfiram
- ritonavir
- sodium valproate
- · acute alcohol intake
- quinupristin

Inducers of the P450 system include:

- antiepileptics: phenytoin, carbamazepine
- · barbiturates: phenobarbitone
- rifampicin
- St John's Wort

- · chronic alcohol intake
- griseofulvin
- smoking (affects CYP1A2, reason why smokers require more aminophylline)

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto- induction

P450 drug interactions: more detail

the most important and common reason for drug interactions is the P450 ${\bf CYP3A4}$ ${\bf system}.$

The table below shows the main enzyme systems that are affected by common drugs.

P450 system	Substrates	Inhibitors	Inducers
СҮРЗА4	Macrolides Antiretrovirals Calcium channel blockers simvastatin	Macrolides Protease inhibitors (including ritonavir) Imidazoles grapefruit juice	Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's Wort
CYP2D6	Tricyclic antidepressants Antipsychotics	SSRIs Ritonavir	
CYP2C9	Warfarin Sulfonylureas	Imidazoles Amiodarone Sodium valproate	Rifampicin
CYP1A2	Theophylline	Ciprofloxacin	Smoking Omeprazole
CYP2E1	Alcohol		Chronic alcohol Isoniazid

Interestingly, **codeine** and **dihydrocodeine** are metabolised by cytochrome **P450 2D6** to morphine, which provides the analgesic effect; therefore, those patients who are CYP-2D6 poor metabolisers will have a reduced analgesic effect with codeine or Dihydrocodeine

CYP-2C8	CYP-2C18/19	CYP-2D6
Omeprazole	Diazepam	Tricyclic antidepressants
Diazepam	Tricyclic antidepressants	β-blockers
Barbiturates	Omeprazole	Dihydrocodeine
	Proguanil	Ecstasy (MDMA)
		Selective serotonin reuptake
		inhibitors

Drug interactions with cytochrome P450

- Drug interactions with the cytochrome P450 system are only clinically significant for drugs that have a narrow therapeutic index (ie small changes in plasma concentrations lead to the drug concentration being either sub-therapeutic or toxic)
- Examples of these drugs include:
 - **⇔** Ciclosporin
 - ⇒ warfarin
 - ⇒ theophylline and
 - ⇒ phenytoin
- Lithium has a narrow therapeutic index owing to changes in absorption and excretion and does not interact with cytochrome P450

Drugs required therapeutic monitoring

Antiepileptics	Antiarrhythmics	Antibiotics Gentamicin Tobramycin Vancomycin
Immunosuppressants	Antimanics • Lithium	Bronchodilators • Theophylline

Drug induced manifestations

Drug causes gingival hyperplasia

Gingival hyperplasia: phenytoin, ciclosporin, calcium channel blockers and AML

Drug causes of gingival hyperplasia

- phenytoin
- Ciclosporin
- calcium channel blockers (especially nifedipine)

Other causes of gingival hyperplasia include

acute myeloid leukaemia (myelomonocytic and monocytic types)

Drugs causing photosensitivity

- thiazides
- · tetracyclines, sulphonamides, ciprofloxacin
- amiodarone
- · NSAIDs e.g. piroxicam
- psoralens
- sulphonylureas

Drugs causing specific skin reactions

- · Psoriatic-type reactions are most commonly caused by beta-blockers
- Antibiotics may cause lupus-type reactions, erythema multiforme, Stevens

 –Johnson syndrome and erythroderma
- Warfarin is associated with alopecia, as are cytotoxic agents and antithyroid agents
- Phenytoin may cause both acne and gingival hyperplasia

Drug affects folic acid metabolism

Drugs which inhibit dihydrofolate reductase are:

- Methotrexate
- · Pyrimethamine, and
- · Trimethoprim.

Drugs which interfere with absorption/storage of folate are:

- Phenytoin
- · Primidone, and
- · Oral contraceptives.

Drug causes SIADH

Didg Called Circle	
most commonly causes SIADH	Other causes
Thiazide diuretics	Chlorpropamide
 Vincristine 	Carbamazepine
 Vinblastine 	Phenothiazines
 Cyclophosphamide 	Tricyclic antidepressants
	Clofibrate
	Oxytocin
	Vasopressin
	Morphine
	Barbiturates
	Nicotine

Drug causes of urticaria

The following drugs commonly cause urticaria:

- aspirin
- penicillins
- NSAIDs
- opiates

Drugs induced galactorrhoea

Drug causes of raised prolactin

- metoclopramide, Domperidone
 - ⇒ Domperidone is a dopamine antagonist producing large rises in prolactin concentrations.
- phenothiazines
- haloperidol
- Cimetidine produces hyperprolactinaemia only when given intravenously (IV).
- · very rare: SSRIs, opioids

Drugs associated with gynaecomastia

- Spironolactone (the most common), causes gynaecomastia by several mechanisms.
 - ⇒ **block androgen production** by inhibiting enzymes in the testosterone synthetic pathway,
 - block receptor binding of testosterone and dihydrotestosterone.
 - ⇒ increases free oestrogen levels by displace oestradiol from sex hormone binding globulin (SHBG)

Other causes

- inhibitors of testosterone synthesis:
 - ⇒ ketoconazole

 - ⇒ etomidate, and
 - ⇒ cisplatin.
- Oestrogens:
 - ⇒ Digoxin → direct action at oestrogen receptors.
- LHRH analogues
- Finasteride.

- marijuana
- heroin
- isoniazid
- Ciclosporin
- · calcium-channel blockers
- ACE inhibitors
- tricyclic antidepressants
- busulphan
- diazepam

Drug-induced impaired glucose tolerance

- Drugs which are known to cause impaired glucose tolerance include:
 - ⇒ thiazides, furosemide (less common)
 - ⇒ steroids
 - ⇒ tacrolimus, ciclosporin
 - ⇒ interferon-alpha
 - ⇒ nicotinic acid
 - ⇒ atypical antipsychotics e.g. olanzapine
- · Beta-blockers an glycemic status:
 - ⇒ beta -2-adrenergic antagonism → inhibition of hepatic gluconeogenesis
 - unselective beta-blockade associated with hypoglycemia (e.g. propranolol rather than the use of beta-1 selective blockers e.g. atenolol, metoprolol).
 - selective beta-1 blockers would not lead to hypoglycaemia however "...in
 patients with abnormal energy requirements or metabolism, administration of
 beta 1-selective-adrenergic antagonists may be associated with
 hypoglycaemia
 - ⇒ Beta-blockers cause a slight impairment of glucose tolerance.
 - ⇒ They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

Drug-induced lupus erythematosus

The most commonly associated drugs

- procainamide
- hydralazine 2,
- · anti-TNF alpha agents,
- statins
- isoniazid
- minocycline.

Drug-induced Pancytopaenia

Trimethoprim may cause pantcytopaenia

Drug causes of Pancytopaenia

- cytotoxics
- · antibiotics: trimethoprim, chloramphenicol
- · anti-rheumatoid: gold, penicillamine
- · carbimazole (causes both agranulocytosis and pancytopaenia)
- anti-epileptics: carbamazepine
- · sulphonylureas: tolbutamide
- Although both azathioprine and mesalazine cause pancytopenia, it is more commonly seen in patients undergoing azathioprine therapy.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (probable immune mediated)

- quinine
- abciximab
- NSAIDS
- · diuretics: furosemide
- · antibiotics: penicillins, sulphonamides, rifampicin
- anticonvulsants: carbamazepine, valproate
- heparin

Sulfa drugs

- Hypersensitivity reactions to sulfa medications are common and are usually limited to pruritic rashes.
- An acronym for remembering sulfa drugs is Popular FACTSSS:
 - ⇒ **P**robenecid.
 - ⇒ Furosemide.
 - ⇒ Acetazolamide,

 - ➡ Thiazides.
 - ⇒ Sulfonamide antibiotics,
 - ⇒ Sulfasalazine,
 - ⇒ Sulfonylureas.
- Furosemide
 - ⇒ Most loop diuretic, such as furosemide are sulfa-containing drugs,
 - ⇒ sulfa-containing drugs can cause interstitial nephritis.
 - Interstitium is the site of furosemide toxicity.
 - For these patients, ethacrynic acid can be used instead, because it does not contain a sulfa group.

Disulfiram

Action

- Alcohol antagonist drug used to treat chronic alcoholism
- Ethanol is metabolized by two enzymes:
 - Alcohol dehydrogenase, which is located in the cytosol, converts ethanol to acetaldehyde.
 - 2. Aldehyde dehydrogenase, which is located in the mitochondria, converts acetaldehyde to acetyl CoA. Both enzymes require NAD+ for function.
- **Disulfiram is an inhibitor of aldehyde dehydrogenase** and causes accumulation of acetaldehyde, leading to severe nausea and vomiting if alcohol is consumed.

Disulfiram reaction

- The elevations in serum acetaldehyde levels cause the <u>symptoms of disulfiram reaction</u> which include:
 - ⇒ flushing,
 - ⇒ headache,
 - ⇒ nausea, vomiting
 - ⇒ sweating
 - ⇒ blurred vision,
 - ⇒ dyspnea,
 - ⇒ palpitations, hypotension, chest pain and syncope.
- avoid all alcohol-containing products (e.g., cough and cold syrups, mouthwash, or foods containing alcohol) while taking this medication.
- Disulfiram typically causes an acute hepatitis like syndrome 2 to 12 weeks after starting the medication that can be severe and lead to acute liver failure or need for liver transplantation.

Disulfiram → inhibitor of Aldehyde dehydrogenase, which is located in the mitochondria Fomepizole → inhibitor of Alcohol dehydrogenase, which is located in the cytosol

The target of disulfiram is located in which cellular compartments?

⇒ Mitochondria

<u>Drug-induced ethanol intolerance (disulfiram-like reaction)</u>

- As in the case with disulfiram, the underlying mechanism is believed to be the accumulation of acetaldehyde in the blood, due to inhibition of the hepatic aldehyde dehydrogenases.
- drugs which can produce DISULFIRAM like reaction when taken with Alcohol:
 - ⇒ chloramphenicol,
 - ⇒ furazolidone.
 - ⇒ nitroimidazole antibiotics, including metronidazole, and
 - ⇒ quinacrine,
 - ⇒ First-generation sulfonylureas, e.g. tolbutamide and chlorpropamide
 - ⇒ cephalosporins, including cefoperazone, cefamandole and cefotetan
 - ⇒ antifungal eg: Griseofulvin
 - ⇒ Procarbazine

Drug-induced long QT

Commonly medications that cause QT prolongation					
class	Examples				
Antiarrhythmic	AmiodaroneDisopyramideIbutilide	ProcainamideQuinidineSotalol			
antipsychotics	ChlorpromazineClozapineHaloperidol	 Quetiapine Risperidone Thioridazine			
antibiotics	AzithromycinClarithromycinErythromycinCiprofloxacinLevofloxacin	 Ofloxacin Trimethoprim – sulpha Ketoconazole Fluconazole itraconazole 			
Antidepressants	AmitriptylineCitalopramDesipramineDoxepinfluoxetine	ImipramineNortriptylineParoxetineSertralinevenlavaxine			
Antiemetics	 Ondansetron 	 prochlorperazine 			

Drugs causing ocular problems

Visual disturbance	cataract	Corneal opacities	Optic neuritis	Retinopathy	Blue tinge in vision	Yellow- green tinge
Drug	steroids	Amiodarone Indomethacin	Ethambutol Amiodarone Metronidazole	Chloroquine, quinine	Sildenafil	Digoxin

Visual changes secondary to drugs

- blue vision: Viagra ('the blue pill')
- yellow-green vision: digoxin

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

Drug induced photosensitivity

Rash on the forearms and face is typical of a photosensitivity rash

- Thiazides
- Tetracyclines, sulphonamides, ciprofloxacin
- Amiodarone

- · NSAIDs e.g. Piroxicam
- Psoralens
- Sulphonylureas

Mnemonic: FAST-N (Fluoroquinolones eg: cipro. Amiodarone. Sulfo. Tetracyclines. NSAIDs)

Drug induced ototoxicity

- Causes
 - ⇒ Aminoglycosides
 - Streptomycin → irreversible cochlear and vestibular dysfunction
 - ⇒ Platinum-based antineoplastic agents,
 - ⇒ Salicylates
 - ⇒ Quinine
 - ⇒ Loop diuretics.
- Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus.
- The time of onset is unpredictable:
 - ⇒ marked hearing loss can occur even after a single dose.
 - ⇒ may occur several weeks or months after completion of antibiotic or antineoplastic therapy.
- · Usually irreversible with most agents.

Drug induced seizures

- Drugs that cause seizures as a drug reaction include:
 - ⇒ Isoniazid (vitamin B6 deficiency)
 - ⇒ Bupropion,
 - ⇒ Imipenem/cilastatin
 - ⇒ Tramadol
 - ⇒ Enflurane

Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane.

With seizures, I BITE my tongue.

<u>Drug causes erythema multiforme, and the Stevens-Johnson syndrome subtype.</u>

- Allopurinol \rightarrow (the Most commonly associated)
- Recent drugs nevirapine, lamotrigine, sertraline, pantoprazole, tramadol
- Antibiotics sulphonamides, co-trimoxazole, penicillin, cephalosporins, fluoroquinolones, vancomycin
- NSAIDs piroxicam, fenbufen, ibuprofen, ketoprofen, naproxen, tenoxicam, diclofenac, sulindac

- Anti-TB rifampicin, ethambutol, isoniazid, pyrazinamide
- Anticonvulsants barbiturates, carbamazepine, phenytoin, valproate, lamotrigine
- Antifungals fluconazole, nystatin, griseofulvin
- · Antidepressants lamotrigine, sertraline.
- Sulfasalazine

Drugs which act on serotonin receptors

- Below is a summary of drugs which are known to act via modulation of the serotonin (5-HT) system.
- It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis.

Agonists

- sumatriptan is a 5-HT1D receptor agonist which is used in the acute treatment of migraine
- ergotamine is a partial agonist of 5-HT1 receptors

Antagonists

- pizotifen is a 5-HT2 receptor antagonist used in the prophylaxis of migraine attacks.
- Methysergide is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis
- cyproheptadine is a 5-HT2 receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome
- ondansetron is a 5-HT3 receptor antagonist and is used as an antiemetic

5HT-2 receptor inhibition

- 5HT-2 receptor inhibition also reduces platelet aggregation
- one example is sarpogrelate developed in North East Asia primarily as an alternative to aspirin because of its association with a lower risk of haemorrhage.

Drugs that can be cleared with Hemodialysis - mnemonic: BLAST

- Barbiturate
- Lithium
- Alcohol (inc methanol, ethylene glycol)
- Salicylates
- Theophyllines (charcoal hemoperfusion is preferable)

Drugs which cannot be cleared with HD include

- Tricyclics
- Benzodiazepines (diazepam, midazolam, alprazolam)
- Dextropropoxyphene (co-proxamol)
- Digoxin, β-blockers

Cardiovascular drugs

Prescribing in patients with heart failure

The following medications may exacerbate heart failure:

- thiazolidinediones: pioglitazone is contraindicated as it causes fluid retention
 - ⇒ pioglitazone is now the only thiazolidinedione on the market
- verapamil: negative inotropic effect
- . NSAIDs & glucocorticoids: should be used with caution as they cause fluid retention
 - ⇒ low-dose aspirin is an exception many patients will have coexistent cardiovascular

disease and the benefits of taking aspirin easily outweigh the risks

- class I antiarrhythmics; flecainide (negative inotropic and proarrhythmic effect)
- Celecoxib (rofecoxib has been withdrawn) acts by inhibiting prostaglandin synthesis via inhibition of cyclo-oxygenase-2 (COX-2). It causes fluid retention and can worsen an already pre-existing heart failure. The CSM reminds prescribers that celecoxib is contraindicated in:
 - ⇒ patients with severe congestive heart failure,
 - ⇒ active peptic ulceration
 - ⇒ or gastrointestinal bleeding.

Antiarrhythmics: Vaughan Williams classification

The Vaughan Williams classification of antiarrhythmics is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and magnesium

AP = action potential

Class	Examples	Mechanism of action	
la	Quinidine Procainamide Disopyramide	Block sodium channels Increases AP duration Notes: Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia) Procainamide may cause drug-induced lupus Disopyramide toxicity → Urinary retention	
lb	Lidocaine Mexiletine Tocainide	Block sodium channels Decreases AP duration	
Ic	Flecainide Encainide Propafenone	Block sodium channels No effect on AP duration	
II	Propranolol Atenolol Bisoprolol Metoprolol	Beta-adrenoceptor antagonists	
III	Amiodarone Sotalol Ibutilide Bretylium	Block potassium channels	
IV	Verapamil Diltiazem	Calcium channel blockers	

Antiarrhythmic agents

- Calcium-channel blockers act mainly on (SA) (AV) nodes (direct membrane effect), as
 these structures are almost exclusively depolarised by the slow calcium channels
- Flecainide binds to the sodium channel and decreases the speed of depolarisation (in other words, decreases conduction velocity) (Slows the upstroke of the action potential)
- Atenolol decreases sympathetic tone
- Amiodarone and sotalol increase the action-potential duration and therefore the refractory periods
 - ⇒ they have little effect on conduction velocity
 - ⇒ Sotalol have a high risk of producing torsades de pointe
- Class V agents (digitalis agents) affect SA and AV nodes by increasing vagal tone

Atropine

Action

Atropine is an antagonist of the muscarinic acetylcholine receptor

Uses

- Treatment of organophosphate poisoning
- Bradycardia, heart block

Physiological effects

- Tachycardia
- Mydriasis
- J Secretions of exocrine glands
- ↓ Tone and motility of smooth muscles (i.e., ↓ urgency in cystitis)
- \(\text{ Cholinergic overactivity in CNS} \)

MRCPUK-part-1-january 2018 exam: Which physiological effect would be expected following administration of atropine? Tachycardia + mydriasis

Adenosine

Adenosine

- dipyridamole enhances effect
- · aminophylline reduces effect

Mechanism of action

- · causes transient heart block in the AV node
- agonist of the A1 receptor which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- Acts on specific adenosine cell surface receptors (A1 and A2)
- Stress testing: A2A adenosine receptor agonist;
 - activation of the A2A adenosine receptor produces coronary vasodilation and increases coronary blood flow
- † coronary vasodilatation (Adenosine is an important mediator of metabolic vasodilatation)
- Increasing O₂ demands are met by → adenosine production → vasodilatation → increased blood supply.
- Adenosine effect on renal
 - ⇒ In the renal vasculature, in contrast, adenosine can produce vasoconstriction
 - ⇒ However, the vasoconstriction elicited by an intravenous infusion of adenosine is

- only short lasting, being replaced within 1-2 min by vasodilatation.
- ⇒ It appears that the steady-state response to the increase of plasma adenosine levels is global renal vasorelaxation that is the result of A2A receptor activation
- Adenosine lowers glomerular filtration rate (GFR) by constricting afferent arterioles, especially in superficial nephrons. In contrast, it leads to vasodilation in deep cortex and medulla.
- ↓↓ sinus node automaticity and AVN conduction.
- adenosine has a very short half-life of about 8-10 seconds
- Inactivated by adenosine deaminase.

Adverse effects

- transient facial flushing (18%) (most common)
- bronchospasm
 - ⇒ Dyspnea (12%)
 - ⇒ It should be avoided in asthmatics
- · choking sensation, where patients often clutch their chest
- chest pain
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

Interaction

- The effects of adenosine are enhanced by dipyridamole (anti-platelet agent)
 - Adenosine transported out of the cell to the extracellular space by specific bidirectional nucleoside transporters. Inhibitors of these transporters, such as dipyridamole, increase the extracellular concentrations of adenosine and are useful clinically to treat certain cardiovascular complications.
- · Adenosine effects blocked by theophyllines.
- Unlike verapamil it may be used following β-blockade

Adenosine is a coronary vasodilator (which is why we use it in cardiac stress testing) and a bronchoconstrictor (action opposed by theophylline).

Flecainide

Action

- Flecainide is a Vaughan Williams class 1c antiarrhythmic.
- It slows conduction of the action potential by acting as a potent sodium channel blocker.
 - ⇒ Slows the upstroke of the action potential
 - ⇒ does not alter the overall length of the action-potential duration.
- This may be reflected by widening of the QRS complex and prolongation of the PR interval

Indications

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

Contraindications

post myocardial infarction → increase mortality

Adverse effects

- negatively inotropic
- bradycardia
- oral paraesthesia
- proarrhythmic
- visual disturbances

Amiodarone

Amiodarone - MOA: blocks potassium channels

- Amiodarone is a class III antiarrhythmic agent
- used in the treatment of atrial, nodal and ventricular tachycardias.
- metabolized in the liver via cytochrome P450 3A4.

Action

- The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential.
 - ⇒ Amiodarone **prolongs the refractory period** of the cardiac conducting system.
 - ⇒ Its antiarrhythmic effects are due mostly to the **inhibition of the rapid component of the delayed potassium rectifier IKr channel** (as with sotalol) but also have an effect on the slow component.
- Amiodarone also has other actions such as blocking sodium channels (a class I effect)

Several factors limit the use of amiodarone:

- long half-life (20-100 days)
 - Because of its long half-life there is a potential for drug interactions to occur for several weeks after amiodarone has been stopped.
- should ideally be given into central veins (causes thrombophlebitis)
- has proarrhythmic effects due to lengthening of the QT interval
- · interacts with drugs commonly used concurrently e.g. Decreases metabolism of warfarin
- · numerous long-term adverse effects.

Monitoring of patients taking amiodarone

- TFT, LFT, U&E, CXR prior to treatment
- TFT, LFT every 6 months
 - ⇒ and for up to 12months after discontinuation of amiodarone
 - ⇒ An increase of up to 40% above the baseline T4 is a normal effect of amiodarone. This occurs approximately 2 months after initiation of therapy & does not require discontinuation.

Administration

300 mg of amiodarone made up to 20 ml with 5% dextrose given as an intravenous bolus is
the drug of choice in treating refractory ventricular fibrillation or pulseless ventricular
tachycardia (100 mg of lidocaine may be given intravenously when amiodarone is
unavailable).

Adverse effects

corneal deposits is the most common side effect

hypothyroidism occur more frequently than hyperthyroidism

- Thyroid dysfunction: both hypothyroidism and hyperthyroidism
 - ⇒ Amiodarone blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) → hypo (occurs in up to 20% of patients taking amiodarone)
 - ⇒ It is also a potential source of large amounts of inorganic iodine → hyper (occurs in 3% of patients in iodine-deficient areas, but in 20% in areas where iodine is sufficient).
- Corneal deposits
 - present in most patients,
 - almost universal in patients taking amiodarone therapy (at least 90%).

- ⇒ rarely interfere with vision, becomes manifest by the presence of night-time visual glare, noticed while driving.
- ⇒ usually reversible on withdrawal of drug
- Photosensitivity
 - ⇒ Skin deposits result in photodermatitis and a greyish-blue discoloration on sun-exposed areas ('slate-grey' appearance (Skin sensitivity)
 - ⇒ can be prevented by using a sun block
- Pulmonary fibrosis/pneumonitis (5-7%).
- Liver cirrhosis/hepatitis
- Peripheral neuropathy, myopathy
- · Prolonged QT interval
- Thrombophlebitis and injection site reactions
- Bradycardia
- Persistent slate-grey skin discoloration (ceruloderma)



- ⇒ more common in males than females.
- ⇒ the pigmentation consists of brownish-yellow deposits of amiodarone, **iron** and others (not including melanin or hemosiderin)
- ⇒ On biopsy of these lesions, which cell type is laden with pigment?
 - → histiocytes of the dermis
- appears in sun-exposed areas and is thought to be activated by an UVA-related hypersensitivity response.
 - Sun exposure is not recommended for patients on amiodarone.
- ⇒ Treatment
 - discontinuation of the drug
 - if not disappeared after discontinuation → laser-based therapy.
- Neutropenia
- Nightmares, sleep disturbance

Important drug interactions of amiodarone

- · Decreased metabolism of warfarin, therefore increased INR
 - ⇒ Decrease warfarin dose by 33- 50% and monitor the INR weekly
- · Increased digoxin levels
 - ⇒ the dose of digoxin should be halved when patients are started on amiodarone.
- There is an increased risk of ventricular arrhythmias when amiodarone is given with tricyclics, hence concomitant use should be avoided.

For amiodarone and the thyroid gland (See Endocrinology chapter)

Dobutamine & Dopamine

	Dobutamine	Dopamine
Action	 Direct Sympathomimetics (β₁ receptor agonist) β₁> β₂, agonist positive inotropic effect chronotropic effects 	 D1 = D2 > β > α Chronotropic effects at lower doses (β effect) Vasoconstriction at high doses (α effect)
Indications	Cardiogenic shockAcute heart failureCardiac stress testing	Heart failureCardiogenic shockUnstable bradycardia

Adrenaline

Adrenaline induced ischaemia - phentolamine

Recommend Adult Life Support (ALS) adrenaline doses

- anaphylaxis: 0.5ml 1:1,000 IM
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Adrenaline is a sympathomimetic amine with **both alpha and beta** adrenergic stimulating properties.

The β- effect will cause significant tachycardia

Indications

- anaphylaxis
- cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses

- anaphylaxis: 0.5ml 1:1,000 IM
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Management of accidental injection

- local infiltration of phentolamine
- An alternative possibility is locally applied GTN paste

Anaphylaxis

- Where there is a history of a typical allergic reaction, current United Kingdom resuscitation guidelines suggest adrenaline if there is:
 - ⇒ Stridor
 - ⇒ Wheeze
 - ⇒ Respiratory distress, or
 - ⇒ Clinical evidence of shock.
- Adrenalin is used for its alpha-agonist effects that include increased peripheral vascular resistance and reversed peripheral vasodilatation, systemic hypotension, and vascular permeability.

- **Beta-agonist effects** include bronchodilatation, chronotropic cardiac activity, and positive inotropic effects.
- IM administration is preferred because of a superior safety profile with respect to cardiac adverse events compared with the IV route, although 1:10000 adrenalin IV may be used in a life-threatening situation.
- The intramuscular (IM) route for adrenaline is the route of choice for most healthcare providers.
- Adult **EpiPen** which allergy sufferers can carry with them contains 0.3 mg or 0.15 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Antiplatelets

Overview of antiplatelet agents

Overview of an	Overview of antiplatelet agents			
Group	Agents	Indications	Adverse effects	
Irreversible cyclooxygen ase inhibitors	Acetylsalicylic acid (aspirin)	Acute coronary syndrome Ischemic stroke Primary and secondary prevention of cardiovascular disease	 Reye syndrome Aspirin exacerbated respiratory disease Gl upset Salicylate toxicity Affects the kidneys in a dose-dependent manner ⇒ Low doses → uric acid retention ⇒ High doses → uric acid excretion 	
P2Y12 receptor antagonists (ADP receptor inhibitors)	ClopidogrelPrasugrelTicagrelorTiclopidineCangrelor	Dual antiplatelet therapy (with acetylsalicylic acid) in ACS Alternative to aspirin	Allergic reactionsHaemorrhageGI upset	
Glycoprotein Ilb/Illa inhibitors	AbciximabEptifibatideTirofiban	High-risk patients with unstable angina/NSTEMI before undergoing PCI	Acute thrombocytopeniaHaemorrhage	

Summary of latest guidance

The table below summarises the most recent guidelines regarding antiplatelets:

Diagnosis	1st line	2nd line
NSTEMI	Aspirin (lifelong) & clopidogrel (12 months)	If aspirin contraindicated, clopidogrel (lifelong)
STEMI	Aspirin (lifelong) & clopidogrel (1m if no/bare stent, 12 m if drug-eluting stent)	If aspirin contraindicated, clopidogrel (lifelong)
TIA*	Clopidogrel (lifelong)	Aspirin (lifelong) & dipyridamole (lifelong)
Ischaemic stroke	Clopidogrel (lifelong)	Aspirin (lifelong) & dipyridamole (lifelong)
Peripheral arterial disease	Clopidogrel (lifelong)	Aspirin (lifelong)

^{*}the guidelines for TIA are based on the 2012 Royal College of Physicians National clinical guideline for stroke. These guidelines corrected the anomaly where patients who've had a stroke were given clopidogrel, but those who'd suffered a TIA were given aspirin + dipyridamole.

Peri-Operative Management of Anticoagulation and Antiplatelet Therapy (British society for Haematology guidelines 2016)

- Warfarin and other vitamin K antagonists
 - ⇒ Emergency surgery in patients on warfarin
 - If surgery can wait for 6–8 h then 5 mg of intravenous phytomenadione can restore coagulation factors;
 - if this is not possible, anticoagulation can be reversed with 25–50 u/kg of fourfactor prothrombin complex concentrate
 - ⇒ Consider bridging with treatment dose heparin in:
 - 1) Patients with a VTE within previous 3 months.
 - 2) Very high risk patients such as patients with a previous VTE whilst on the appearance anticoagulation who now have a target INR of 3.5.
 - 3) Patients with a previous stroke/TIA in last 3 months.
 - 4) Patients with a previous stroke/TIA and three or more of the following risk factors:
 - Congestive cardiac failure
 - ❖ Hypertension (>140/90 mmHg or on medication)
 - ❖ Age >75 years
 - Diabetes mellitus
 - 5) mechanical heart valve (MHV) patients other than those with a bileaflet aortic valve and no other risk factors
 - ⇒ the post-operative bridging (i.e. full dose anticoagulation) should not started until <u>at least 48 h after high bleeding risk surgery</u> although thromboprophylaxis should be given if indicated.
 - Warfarin should be stopped for <u>5 days before an elective procedure</u> if anticoagulation needs to be discontinued
- Antiplatelet therapy
 - spirin monotherapy (for secondary prevention of cardiovascular disease) can be continued for most invasive non-cardiac procedures
 - ⇒ Aspirin can be continued both before and after coronary artery bypass surgery

The lifespan of a platelet is 7–10 days. If aspirin is held prior to surgery, it should be discontinued one week in advance.

Acetylsalicylic acid (ASA, aspirin)

Aspirin is a common cause of urticaria

Overview

- Aspirin works by blocking the action of both cyclooxygenase-1 and 2.
- Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis.
- Cyclo-oxygenase is an enzyme that converts arachidonic acid to thromboxane A2 (TXA2), a strong platelet agonist
- Because the platelet has no protein synthetic apparatus the effects of aspirin are irreversible and last for the life of the platelet (8-10 days)
- † bleeding time (PT and PTT unchanged)
- The blocking of thromboxane A2 formation in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease.
- Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case.

Mechanism of action

- ASA covalently attaches an acetyl group to COX.
- Irreversible COX-1 inhibition → inhibition of thromboxane (TXA2) synthesis in platelets → inhibition of platelet aggregation (antithrombotic effect)
- Onset of antiplatelet action: within minutes
- Duration of antiplatelet action: 7–10 days
- Irreversible COX-1 and COX-2 inhibition → inhibition of prostacyclin and prostaglandin synthesis → antipyretic, anti-inflammatory, and analgesic effect

Effects

- Low dose (below 300 mg/day): inhibition of platelet aggregation
- Intermediate dose (300-2400 mg/day): antipyretic and analgesic effect
- High dose (2400-4000 mg/day): anti-inflammatory effect

What do the *current* guidelines recommend?

- first-line for patients with ischaemic heart disease
- Current NICE guidelines advise that people with acute upper gastrointestinal bleeding
 who take aspirin for secondary prevention of vascular events and in whom
 haemostasis has been achieved continue on low dose aspirin.
- the U.S. Preventive Services Task Force (USPSTF), recommended that, for some people, aspirin can be used to help reduce their risk of cardiovascular disease and colorectal cancer.

Potentiates

- oral hypoglycaemics
- warfarin
- steroids

Reye syndrome

- Definition: a rare type of hepatic encephalopathy that is associated with aspirin use for viral illness in children < 19 years
- Aetiology: aspirin use in individuals < 19 years of age with a febrile illness
- Pathophysiology
 - ⇒ accumulation of salicylate metabolites in the liver → mitochondrial injury and reversible inhibition of enzymes required for fatty acid oxidation; acute encephalopathy
 - ⇒ Hyperammonemia → cerebral edema → ↑ ICP
- Features
 - ⇒ Preceding viral infection (e.g., influenza, varicella or viral gastroenteritis)
 - ⇒ Acute encephalopathy
 - ⇒ Severe vomiting
 - ⇒ coma
 - ⇒ Liver failure
 - ⇒ Fatty degeneration
 - ⇒ Hepatomegaly
- Diagnostics: clinical diagnosis; further testing to rule out other causes (diagnosis of exclusion)
 - ⇒ ↑ AST and ALT
 - ⇒ Hyperammonemia
 - ⇒ Hypoglycemia
 - ⇒ Liver biopsy: microvesicular hepatic steatosis
- Prevention
 - ⇒ Aspirin should be avoided in individuals < 19 years of age
 </p>
 - ⇒ Exception: children with Kawasaki disease
- Prognosis → Mortality rate: ~ 20%

In hypersensitive patients aspirin can cause:

- Angioedema
- · Bronchospasm, and
- · Urticaria (skin rashes).

ASA can be continued normally if patient is going for dental procedure

Avoid aspirin in children < 16 years as risk of Reye's syndrome

Aspirin is not considered to be safe in breast-feeding due to the risk of causing Reye's syndrome in the baby.

Salicylate overdose

The mixed respiratory alkalosis and metabolic acidosis in a sweaty, confused patient point towards salicylate overdose.

The development of pulmonary edema suggests severe poisoning and is an indication for hemodialysis.

Tinnitus is characteristic and salicylate toxicity may produce deafness.

Overview

- A key concept for the exam is to understand that salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis.
 - ⇒ Early stimulation of the respiratory centre leads to a respiratory alkalosis
 - ⇒ later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis.
- The metabolic acidosis can increase the transfer of salicylates across the blood-brain barrier, thereby increasing CNS toxicity

Features

- Early features:
 - ⇒ hyperventilation (centrally stimulates respiration) → respiratory alkalosis
 - the most prominent feature of the early period after aspirin overdose
 - ⇒ tinnitus: typically occurs at plasma salicylate concentrations above 400-500 mg/l
 - ⇒ vertigo
 - ⇒ letharqy
 - ⇒ sweating, pyrexia
 - salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production
 - ⇒ peripheral vasodilatation and bounding pulse
 - ⇒ nausea/vomiting → dehydration
- Later features:
 - ⇒ metabolic acidosis
 - by uncoupling oxidative phosphorylation, leading to a build- up of organic acids in the blood.
 - ⇒ hyperglycaemia and hypoglycaemia
 - Hypoglycaemia is commonly seen in children but not in adults
 - ⇒ seizures
 - ⇒ coma
 - Although decreased consciousness is seen in aspirin overdose, it is seen late, and is associated with severe metabolic acidosis and hypokalaemia.
 - Early presentation with coma will suggest that another drug has been taken in addition to aspirin.

Treatment

- No specific antidote
- The management is supportive, with measures to prevent further absorption from the gastrointestinal tract and enhance excretion.
- General (ABC, charcoal) Multi-dose activated charcoal may be indicated

⇒ activated charcoal should be repeated as bezoars may form, resulting in delayed absorption of salicylate. This **should continue until salicylate levels have peaked.**

· Urinary alkalinization

- ⇒ alkalinisation of the urine should be considered in patients with a plasma level > 300 mg/L.
- ⇒ urine and serum alkalinization through intravenous sodium bicarbonate (1.25% or 8.4%)
- ⇒ By alkalinizing the urine, charged salicylic acid will become protein bound and secreted through the proximal tubule, which minimizes the diffusion of uncharged salicylate back into the renal epithelium.
 - The ionisation of a weak acid, such as salicylic acid, is increased in an alkaline environment.
 - The administration of an intravenous infusion of sodium bicarbonate aiming for a urinary pH of 7.5-8 will increase the excretion of the acid 10-fold.
- ⇒ Alkalinization of the serum further promotes diffusion of salicylate out of the brain.
- Haemodialysis
 - ⇒ Indications for haemodialysis in salicylate overdose
 - serum concentration > 700mg/L
 - metabolic acidosis resistant to treatment
 - acute renal failure
 - pulmonary oedema
 - neurological impairment (coma, hallucinations or seizures)

Clopidogrel

- Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease.
- Clopidogrel belongs to a class of drugs known as thienopyridines which have a similar mechanism of action. Other examples include:
 - ⇒ prasugrel
 - ⇒ ticagrelor
 - ⇒ ticlopidine

Mechanism (Inhibition of the platelet ADP receptor)

 antagonist of the P2Y₁₂ adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets

Indications

- clopidogrel is used in addition to aspirin in patients with an acute coronary syndrome. The dose is 300 mg.
- NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease.
- Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole

Interactions

- concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009)
- this advice was updated by the MHRA in April 2010, evidence seems inconsistent but omeprazole and esomeprazole still cause for concern. Other PPIs such as lansoprazole should be OK

Clopidogrel

- action → antagonist of the P2Y12 adenosine diphosphate (ADP) receptor, inhibiting the
 activation of platelets
- other members of the same class (thienopyridines):
 - ⇒ prasugrel
 - ⇒ ticagrelor
 - ⇒ ticlopidine
- Indications → 1st line for : ACS, an ischaemic stroke, TIA and peripheral arterial disease.
- Interaction → most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK

Prasugrel

- a third-generation thienopyridine antiplatelet agent
- ADP receptor inhibitors
- · advantages compared with clopidogrel
 - ⇒ faster onset of action,
 - ⇒ greater potency in the inhibition of adenosine-induced platelet aggregation,
 - ⇒ more consistent antiplatelet response
- Prasugrel is contra-indicated in patients with prior transient ischaemic attack or stroke.
 - ⇒ In the TRITON-TIMI 38 trial, patients in this group had a higher rate of stroke when taking Prasugrel compared with those taking Clopidogrel.

Ilb/Illa inhibitors (eg: Abciximab)

- Other members of this drug group
 - ⇒ abciximab
 - ⇒ eptifibatide
 - ⇒ tirofiban
- Action
 - monoclonal antibody antagonizes IIb/IIIa glycoprotein receptor on activated platelets
- · prevents platelet aggregation
- Abciximab is a humanised monoclonal antibody

Phosphodiesterase III (PDE) inhibitors (dipyridamole & cilostazol)

Dipyridamole is a non-specific phosphodiesterase inhibitor and decreases cellular uptake of adenosine

Dipyridamole may provoke bronchospasm. Avoid in asthmatics.

Mechanism of action

- inhibits phosphodiesterase → increase platelet cAMP (due to decreased breakdown of cAMP) → reduce intracellular calcium levels → inhibition of platelet aggregation.
- direct arterial vasodilation
 - ⇒ inhibits cellular uptake of adenosine → more available to act on coronary vessels → vasodilation
- · inhibition of thromboxane synthase

Indications

- Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack
- <u>Cilostazol</u> is currently licensed for the management of patients with intermittent claudication without rest pain and with no signs of tissue necrosis.
 - ⇒ It is a first-line medication for the treatment of claudication caused by peripheral artery disease (PAD).
 - ⇒ Trials show an improvement in time to initial pain on walking and maximal walking distance when compared to placebo.
 - ⇒ metabolised by cytochrome P450 3A4.

Contraindications

- known bleeding tendencies (e.g. active peptic ulcer disease, previous haemorrhagic stroke in the last 6 months).
- Asthmatics (may provoke bronchospasm)

Angiotensin-converting enzyme (ACE) inhibitors

Mechanism of action

· Inhibit the conversion angiotensin I to angiotensin II

Indications

- hypertension
 - first-line treatment in younger patients with hypertension and are also extensively used to treat
 - ⇒ less effective in treating hypertensive Afro-Caribbean patients.
- diabetic nephropathy
- heart failure.
- · secondary prevention of IHD.

Side-effects

- Cough:
 - ⇒ occurs in <u>around 15% of patients</u>
 - ⇒ may occur up to a year after starting treatment.
 - ⇒ Thought to be due to increased bradykinin levels
 - The enzyme ACE is also responsible for the metabolism of bradykinin in mast cells and ACEi leads to its bradykinin accumulation
 - ⇒ This phenomenon is not seen in subjects taking angiotensin receptor blockers such as losartan.
- Angioedema:
 - ⇒ may occur up to a year after starting treatment
 - ⇒ ACE inhibitors are the most common cause of drug-induced angioedema

(swelling of his lips and tongue)

- Hyperkalaemia
- ACEi → dilate the efferent arteriole of the glomerulus, → \(\precedeg \) GFR → ↑ creatinine and BUN.
- 1st-dose hypotension: more common in patients taking diuretics

Cautions and contraindications

- Pregnancy and breastfeeding avoid (ACEi & ARB → renal dysgenesis in the fetus)
 Exposure to ACE inhibitors in the first trimester → showed a significant increase in major (in particular, cardiovascular) congenital malformation.
- Renovascular disease significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- Aortic stenosis may result in hypotension
- Patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) signficantly increases the risk of hypotension
- · Hereditary of idiopathic angioedema
- The co-administration of a potassium-sparing diuretic and an ACE inhibitor, may result in profound hyperkalaemia. Thus patients on both these drugs should have their potassium monitored closely.

Monitoring

- Urea and electrolytes should be checked before treatment is initiated and after increasing dose
 - ⇒ Monitoring of renal function and potassium is important after commencement of an ACE inhibitor.
 - The optimum period to check this is one to two weeks after commencing the medication.
- A rise in the creatinine and potassium may be expected after starting ACE inhibitors.
 - ⇒ Acceptable increases are an increase in serum <u>creatinine</u>, up to 50% from <u>baseline or up to 265µmol/l</u> (whichever is smaller) and an increase in <u>potassium up to 5.5 mmol/l</u>.
 - ⇒ NICE guidelines state that when initiating ACE inhibitor therapy a 25% reduction in the eGFR or 30% increase in the serum creatinine is tolerable and should not lead to changes in dosing.
 - ⇒ ACE inhibitors should also be stopped or dose adjusted if is there is a rise in the serum potassium level to greater than 6 mmol/l.
 - ⇒ Other causes of a deterioration in renal function should be excluded first before stopping the ACE inhibitor.
 - e.g: patient taking trimethoprim
 - ❖ This drug competes with creatinine for excretion in the nephron → ↑ serum creatinine.
 - the appropriate option would be to re-check the blood tests in one to two weeks once trimethoprim has been discontinued to see whether the level of renal dysfunction is sustained or improves.

Usage of ACEi & ARB as combination (NICE January 2015)

- Do not combine an ACE inhibitor with an ARB to treat hypertension.
- no significant benefits of ACEi & ARB combination were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function.
- The NICE guideline on <u>chronic heart failure</u> recommends that, after seeking specialist
 advice, the addition of an ARB licensed for heart failure is an option that could be
 considered for people who remain symptomatic despite optimal therapy with an ACE

inhibitor and a beta-blocker

- ⇒ Candesartan and valsartan are the only ARBs licensed as add-on therapy to ACE inhibitors in this situation.
- ⇒ Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in combination with nitrate.

direct renin inhibitors

- Aliskiren (branded as Rasilez) → Direct renin inhibitor
- Action: by inhibiting renin blocks the conversion of angiotensinogen to angiotensin I
- indication: only current role would seem to be in patients who are intolerant of more established antihypertensive drugs
- no trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces blood pressure to a similar extent as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists
- adverse effects were uncommon in trials although diarrhoea was occasionally seen

Other notes

- Enalapril is a prodrug for enalaprat, the active agent
- irbesartan : the dose response is linear, as such dose can be titrated more easily from a base of 75 mg to a maximum of 300 mg.

Adrenoceptor antagonists

Doxazosin is an α-1 adrenoceptor antagonist used in the treatment of hypertension and benian prostatic hypertrophy

Alpha antagonists

- alpha-1: doxazosin
 - ⇒ cause → orthostatic hypotension
- alpha-1a: tamsulosin acts mainly on urogenital tract
- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease) Phenoxybenzamine → presurgical management of hypertension in phaeochromocytoma.

Beta antagonists

- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

Beta-blockers

3 Generations of beta-blockers

	Properties	Drugs
1¤ Generation	Non-selective No vasodilatation	Propranolol, Timolol, Pindolol, Nadolol, Sotalol
2 nd Generation	β1-selective without vasodilation β1selective with vasodilation	Atenolol, Bisoprolol, Metoprolol Nebivolol, Acebutolol
3 rd Generation	Non-selective with vasodilation	Carvedilol, Bucindolol

Indications

- angina
- post-myocardial infarction
- Heart failure: there is now strong evidence that certain beta-blockers improve both symptoms and mortality. Especially Bisoprolol
- arrhythmias: beta-blockers have now replaced digoxin as the rate-control drug of choice in atrial fibrillation
- hypertension: the role of beta-blockers has diminished in recent years due to a lack of evidence in terms of reducing stroke and myocardial infarction.
- thyrotoxicosis
- · migraine prophylaxis
- anxiety

Beta- blocker in heart failure

- NICE recommends β blockers in all HF patients.
- In chronic obstructive pulmonary disease (COPD) patients with HF, cardioselective β blockers appear safer at **lower doses** than higher doses or non-selective β blockers.
- Bisoprolol 5 mgs is too high an initial starting dose, a low dose can always be titrated up later, if tolerated. (starting dose → Bisoprolol 1.25 mg od)
- Carvedilol though effective treatment for heart failure is not selective and therefore carries a
 greater risk of causing bronchospasm.
- Atenolol though cardioselective has no clinical evidence for prognostic benefit in heart failure
- The patient should be closely monitored for deterioration in lung function postadministration.

Examples

Atenolol

- ⇒ Atenolol is a water soluble beta-blocker.
- ⇒ taken once daily
- ⇒ not associated with drowsiness/sleep disturbance like the lipid-soluble beta-blockers.

Propranolol

- ⇒ one of the first beta-blockers to be developed.
- ⇒ Lipid soluble therefore crosses the blood-brain barrier

Nebivolol

- ⇒ has a vasodilatory action in addition to β-blocking effects
- associated with a lower incidence of erectile dysfunction compared with other β-blocking agents
- Bisoprolol \rightarrow the most cardio-selective beta-blocker

Metoprolol

- ⇒ The most lipid-soluble and therefore has the largest volume of distribution
- ⇒ ↑lipid solubility → greater penetration across the blood-brain barrier (and also into other tissues), and therefore a greater incidence of night terrors
- Maximal gastrointestinal absorption of drugs occurs when there is intermediate lipid and water solubility, so that drugs with greater lipid solubility, although allowing greater tissue penetration, may be more poorly absorbed
- ⇒ Metoprolol though selective is shorter acting.
- Oxprenolol → has an intrinsic sympathomimetic properties.

Carvedilol	Bisoprolol
Not β1- selective	Highly β1- selective
Vasodilatation due to α-1- blockade	No α-1- blocking activity
Lipids effects Positive lipid effect → ↑↑HDL & ↓↓LDL Negative lipid effect → ↑↑ cholesterol , TG, VLDL	Lipid profile almost not affected
Oral bioavailability of digoxin increased	No interaction with other CV drugs known
Sensitive to liver enzyme induction	Not sensitive to liver enzyme induction
Extensive metabolism in the liver (CYP2D6)(dose adjustment in liver impairment)	No dose adjustment required

Side-effects

- bronchospasm
- cold peripheries
- β-Blockers cause a rise in peripheral vascular resistance due to the unopposed αadrenoceptor effects (vasoconstriction)
- Fatigue
 - ⇒ fatigue is a frequent side effect
 - ⇒ typically is felt two hours and beyond after taking the drug.
- · sleep disturbances, including nightmares
- β-blockers associated with increased dreams/possible night terrors

Contraindications

- · uncontrolled heart failure
- asthma
- · sick sinus syndrome
- concurrent verapamil use: may precipitate severe bradycardia
- There is a theoretical risk of intrauterine growth retardation with the use of atenolol in pregnancy although the studies which showed this effect were done with very large doses of atenolol.

Beta-blocker overdose

Beta-blocker overdose management: atropine + glucagon

Features

- bradycardia
- · heart failure
- hypotension
- syncope

Management

- · if bradycardic then atropine
- in resistant cases glucagon may be used
- Glucagon acts by bypassing the blocked β-receptor, thus activating adenyl cyclase →
 formation of cyclic AMP from ATP. Cyclic AMP in turn exerts a direct stimulant action on the
 heart.
- The action of glucagon, essential for reversing the effect of beta-blocker overdose → Promotes the formation of cyclic AMP.
 - ⇒ Doses of glucagon used are much higher than those conventionally used for reversing hypoglycaemia in diabetes, with a bolus of 3-10 mg being required, then 2-5 mg/hr by infusion.
- Haemodialysis is not effective in beta-blocker overdose

Calcium channel blockers

Calcium channel blockers - side-effects: headache, flushing, ankle oedema

- Voltage-gated calcium channels are present in:
 - 1. myocardial cells,
 - 2. cells of the conduction system and
 - 3. cells of the vascular smooth muscle.
 - (they have no effect on veins).
- The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

Examples	Indications & notes	Side-effects and cautions
Verapamil	 Angina, hypertension, arrhythmias Highly negatively inotropic Should not be given with beta-blockers as may cause heart block 	Heart failure,constipation,hypotension,bradycardia, flushing
Diltiazem	 Angina, hypertension Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers 	Hypotension,bradycardia,heart failure,ankle swelling
Nifedipine, amlodipine, felodipine (dihydropyridines)	 Hypertension, angina, Raynaud's Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure 	Flushing,headache,ankle swelling

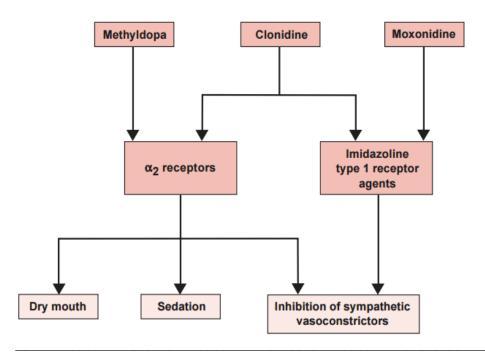
- What is the conventional cardiac micro-anatomical structure targeted by calciumchannel blockers?
 - **⇒** L-type calcium channels
 - all conventional calcium-channel blockers work on L-type calcium channels
 - The L-type channels are found on a tubular network of invaginations of sarcolemma of muscle fibres called T (transverse) tubules.
 - T tubules contain 2 main types of calcium channels:
 - L-type calcium channels (where calcium channel blocker do interact)
 - T (transient) type calcium channels (conventional calcium channel blockers have no effect here).

Centrally acting antihypertensives

Methyldopa → not utilised in a patient with abnormal LFTs

Examples of centrally acting antihypertensives include:

- methyldopa: used in the management of hypertension during pregnancy
- moxonidine: used in the management of essential hypertension when conventional antihypertensives have failed to control blood pressure
- clonidine: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre



Bosentan

- Bosentan is a competitive antagonist of both endothelin-A (ETa) and endothelin-B (ETb)
 receptors, leading to falls in both pulmonary and systemic vascular resistances without an increase
 in heart rate
- effective in patients with pulmonary arterial hypertension
- It is excreted in bile following metabolism by the cytochrome P450 enzymes and this is a potential source of interaction with drugs metabolised by the same isoenzyme
- Common unwanted effects include

 - ⇒ hypotension

 - ⇒ Haemoglobin concentrations can **fall** by up to 1 g/dl during bosentan treatment
 - ⇒ Hepatotoxicity:
 - The most serious unwanted effect is dose-dependent hepatotoxicity, and it is therefore contraindicated in patients with moderate to severe liver disease
 - Generally, hepatotoxicity occurs within the first 3-4 months of treatment
 - ⇒ teratogenic and therefore contraindicated in pregnancy

Nitroglycerin

- Nitroglycerin products are both venous capacitance dilators and coronary and systemic artery dilators
- Administration of nitroglycerin results in:

 - ⇒ decreased myocardial wall tension
 - ⇒ decreased oxygen demand

 - ⇒ increased coronary blood flow to the subendocardium
 - ⇒ reduced afterload
 - ⇒ reduced preload
 - ⇒ increased ventricular compliance
- Nitrates may cause→ haemolytic anaemia

Nicorandil

Action

- · acts through the opening of potassium channels.
- Nicorandil is an activator of ATP-dependent potassium channels
- Effect → relaxation of smooth muscle in veins → venodilatation → ↓ ventricular filling pressures + dilatation of the coronary arterioles
- It relaxes vascular smooth muscle through membrane hyperpolarisation via increased transmembrane potassium conductance and, like nitrates, through an increase in intracellular cyclic guanosine monophosphate (GMP).

Indication

- now second-line treatment for angina
- Use nicorandil for treatment of stable angina only in patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or intolerance to first line anti-anginal therapies such as beta-blockers or calcium antagonists

Side effects

- Headache
 - ⇒ **The most common** unwanted effect (- 35% of patients),
 - ⇒ appears to be dose-dependent
 - ⇒ resolves with continued treatment
- Ulcerations
 - ⇒ oral ulceration, flushing and gastrointestinal disturbances
 - (ulceration of the upper and lower gastrointestinal tract and may present with life threatening bleeding)
 - ⇒ Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess

Contraindication

Use with phosphodiesterase inhibitors such as sildenafil is contraindicated since they can
potentiate the hypotensive effects of nicorandil

Digoxin and digoxin toxicity

The half-life of digoxin is around 36-48 hours. This results in a delay before steady plasma levels are seen, it may take a week to start its action

Digoxin - inhibits the Na⁺/K⁺ ATPase pump

- Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation.
- As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.
- · digoxin is highly water-soluble
- Digoxin has a high volume of distribution and long half-life (36-48 h), which means that loading doses are required to allow the drug to reach a steady-state concentration more quickly.
 - ⇒ If initiated on a maintenance dose (without loading), it will take several days to reach a steady state.
- Digoxin is almost exclusively renally cleared; as a result, renal impairment will significantly alter the half-life of this medication.

Mechanism of action

- decreases conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter
- Increases the force of cardiac muscle contraction due to inhibition of the Na⁺/K⁺ATPase pump which is located in the sarcolemmal membrane.
- Also stimulates vagus nerve

What is the pharmacokinetic reason that drives the practice of loading with digoxin?

- → Volume of distribution.
- The volume of distribution for Digoxin is very large (510 litres). This means that administered doses are rapidly distributed to body tissues.
- The initial distribution lasts for some 6-8hrs, which drives the typical loading regimen for Digoxin of two larger doses (500mcg) some 6-12hrs apart.
- Without loading Digoxin typically takes a few days to reach therapeutic effect.

Digoxin can worsen hyperkalaemia

 Translocation of potassium from the cells into the extracellular space can occur from digoxin overdose due to its dose-dependent Na-K-ATPase pump inhibition.

Drug Interactions Associated with Digoxin

Drug	Effect*	Mechanism
Quinidine	Increase	Decreases renal clearance of digoxin
Verapamil, diltiazem	Increase	Decreases renal clearance of digoxin
Cholestyramine, colestipol	Decrease	Binds digoxin in gastrointestinal tract; interferes with enterohepatic circulation
Spironolactone	Increase	Inhibits tubular secretion of digoxin
Thiazides, furosemide	Increase	Diuretic-induced hypokalemia and/or bumetanide hypomagnesemia potentiates digitalis action

^{*}Increase indicates enhances digitalis effect; decreases diminishes digitalis effect.

Digoxin toxicity

- Plasma concentration alone does not determine whether a patient has developed digoxin toxicity.
- The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.
 - > Samples taken after 6 h will be more accurate in estimating the body's digoxin
- the mechanism of action leading to tachy-arrhythmias in digoxin toxicity → Inhibition of the sodium pump

Features

- · generally unwell, lethargy, anorexia,
 - ➤ The earliest features of digitalis toxicity include: Nausea, vomiting, anorexia.
- · cholinergic effects: nausea, vomiting, diarrhea
- · confusion,
- vellow-green vision
- arrhythmias (e.g. AV block, bradycardia)
 - (Digoxin toxicity can result in any abnormal cardiac rhythm <u>except</u> type-II second-degree atrioventricular (AV) block)

Precipitating factors

- classically: hypokalaemia
 - ➤ (hyperkalaemia may also worsen digoxin toxicity, although this is very small print)
- increasing age
- · renal failure
- myocardial ischaemia
- hypomagnesaemia,
- hypercalcaemia,
- hypernatraemia,
- acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- amyloidosis

- drugs: amiodarone, quinidine, verapamil, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), ciclosporin. Also drugs which cause hypokalaemia e.g. thiazides and loop diuretics
 - Bumetanide is a loop diuretic and may cause hypokalaemia as a side effect. The potassium loss caused by bumetanide increases the toxicity of digoxin.

Management

Antidote "KLAM"

- slowly normalize K+
- Lidocaine
- digoxin Antibodies (anti-dig Fab fragments)
- Mq2+

Phenytoin may be used as an alternative to lidocaine (both are class IB agents) if immune therapy is unsuccessful or unavailable in the treatment of tachyarrhythmias secondary to digoxin toxicity.

- Treatment of digoxin toxicity should be guided by the patient's signs and symptoms and the specific toxic effects and not necessarily by digoxin levels alone.
- Activated charcoal if presented within 1 h of an overdose
 - ➤ The first-line treatment for acute ingestion is repeated dosing of activated charcoal to reduce absorption and interrupt enterohepatic circulation.
- Binding resins (eg, cholestyramine)
 - may bind enterohepatically-recycled digoxin.
 - may be more appropriately used for treatment of chronic toxicity in patients with renal insufficiency.
- · correct arrhythmias
- severe sinus bradycardia (hemodynamically unstable bradyarrhythmic patients) → Atropine
- ventricular tachycardia → responds best to digoxin immune therapy, but phenytoin and lidocaine are useful if immune therapy is ineffective or unavailable.
 - > These drugs depress the enhanced ventricular automaticity without significantly slowing AV conduction
- Magnesium sulfate, 2 g IV over 5 minutes, has been shown to terminate dysrhythmias in digoxin-toxic patients with and without overt cardiac disease.
 - Magnesium is contraindicated in the setting of bradycardia or AV block and should be used cautiously in patients with renal failure.
- Premature ventricular contractions (PVCs), bigeminy, or trigeminy may require only observation unless the patient is hemodynamically unstable, in which case lidocaine may be effective.
- Digibind
 - Its brand name of Digoxin immune fab or Digoxin-specific antibody is an antidote for overdose of digoxin
 - ➤ Action: bind to the digoxin → unable to bind to its action sites
 - > is an immunoglobulin fragment that binds with digoxin.
 - > first-line treatment for significant dysrhythmias from digitalis toxicity
 - ⇒ Indications for digoxin-specific antibodies include:
 - Hemodynamically unstable arrhythmia
 - Tachyarrhythmias with hypotension
 - bradycardia with hypotension that do not respond to atropine

treatment.

- End organ damage
- digoxin level > 4ng/ml if chronic ingestion
- digoxin level > 10 ng/ml if acute ingestion (taken 6 h after the last dose)
- Hyperkalaemia (if not respond to insulin-dextrose infusions): potassium > 5 mEq/L and symptomatic
- ➤ SE → Serum sickness
- If digoxin-specific antibodies not available → lidocaine or phenytoin
- Digoxin toxicity related ventricular tachycardia:
 - Phenytoin and lidocaine are useful for ventricular tachycardia if immune therapy is ineffective or unavailable
 - Phenytoin is thought to suppress the pro-arrhythmic properties of digoxin without diminishing its inotropic effects.
 - lidocaine is useful for chemical cardioversion of digoxin toxicity related ventricular tachycardia. This is because it can reduce ventricular automaticity without significantly slowing AV conduction.
 - Calcium channel blockers are contraindicated because they may increase digoxin levels.
 - Amiodarone is shown to increase digoxin levels and as such can worsen the risk of rhythm disturbance further.
 - VT in digoxin toxicity is resistant to electrical cardioversion, which may actually precipitate VF and asystole.
 - > Bretylium is contraindicated in the treatment of digoxin induced arrhythmias as it can actually precipitate ventricular tachycardia.
 - Quinidine worsens AV and SA conductivity and reduces digoxin tissue binding and is therefore also contraindicated.
- · conventional dialysis is ineffective
- monitor potassium
 - ⇒ Electrolytes
 - In acute toxicity, hyperkalemia is common
 - Although calcium is often used to ameliorate cardiac toxicity from hyperkalemia, it is not recommended in patients with digoxin toxicity because it can delay after-depolarization and may precipitate ventricular tachycardia or fibrillation. This is based on the fact that intracellular calcium levels are already high in this setting.
 - ♦ potassium level > 5 mEq/L → digoxin Fab fragments
 - Chronic toxicity is often accompanied by hypokalemia and hypomagnesemia
 - Concomitant hypomagnesemia may result in refractory hypokalemia
 - Correction of electrolyte imbalances may reverse dysrhythmias.

Which measurement would be most useful when monitoring patient for digoxin efficacy?

→ Pulse rate

 Measuring drug plasma concentration will tell you whether digoxin is at therapeutic concentrations in the blood, but not whether it is having a therapeutic effect.

Diuretics

Class	Compound	Action	Side effects
Loop Diuretics	Furosemide Bumetanide ethacrynic acid	inhibit NKCC2 in the thick ascending loop of Henle	Deafness
Thiazides	hydrochlorothiazide, indapamide	inhibit NaCI co-transporter in early distal tubule	hyponatraemia, hypokalaemia, hypercalcaemia
K+ sparing agents	spironolactone	Aldosterone receptor antagonist	Hyperkalemia
	amiloride, triamterene	inhibit Na channel in late distal tubule	Hyperkalemia
Osmotic Diuretics	mannitol	Inhibit water reabsorption throughout the tubules, but mostly in the proximal tubule	Pulmonary edema

Loop diuretics

Action

- Furosemide and bumetanide are loop diuretics that act by inhibiting the Na-K-Cl cotransporter (NKCC) in the thick ascending limb of the loop of Henle, reducing the absorption of NaCl.
- There are two variants of NKCC; **loop diuretics act on NKCC2**, which is more prevalent in the kidneys.

Indications

- heart failure: both acute (usually intravenously) and chronic (usually orally)
- resistant hypertension, particularly in patients with renal impairment

Adverse effects

- hypotension
- hyponatraemia
- hypokalaemia
- hypochloraemic alkalosis
- ototoxicity

- hypocalcaemia
- renal impairment (from dehydration + direct toxic effect)
- hyperglycaemia (less common than with thiazides)
- gout
- Loop diuretics induces ototoxicity by affecting Na+/K+/2Cl- cotransporters present in the inner ear.
- Explanation of respond to i.v furosemide but not oral in heart failure → Increased bioavailability
 - ⇒ In right heart failure → The patient has a lot of gut oedema which would → reduce the absorption of oral furosemide. Intravenous furosemide would have a much better bioavailability and thus therapeutic effect.
 - ⇒ Protein binding of drugs may be reduced in elderly patients, this may be due to malnutrition.
- Explanation of not responding to furosemide in chronic kidney disease (CKD) → Tubular secretion of furosemide is reduced in CKD
 - Organic acids accumulate in renal failure and compete for tubular secretion with furosemide. This competition can be overcome by using a larger dose of the drug.

A 76-year-old lady taking perindopril 2 mg, bisoprolol 1.25 mg and had recently had her dose of furosemide increased from 40 mg to 80 mg. C/O dizziness, particularly when standing upright after being seated. There were no clinical signs of cardiac failure. Serum urea: 13.3 mmol/L. **Serum creatinine: 221** µmol/L. What is the next step in her management?

- → Stop the furosemide temporarily and restart at a lower dose within a few days
 - This lady is developing postural hypotension after the recent increase in furosemide dose.
 - She has moderate renal impairment.
 - Stopping either her beta-blocker or ACE inhibitor is not the best option for treatment at this stage.

Which loop diuretic is known to cause sulfa-drug allergy?

→ Furosemide

Which loop diuretic is used for diuresis in patients allergic to sulfa drugs?

→ Ethacrynic Acid

Bendroflumethiazide

Bendroflumethiazide - site of action = proximal part of the distal convoluted tubules

the target of action of thiazide diuretics → NaCl co-transporter the target of action of loop diuretics → NKCC2

- Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT).
- The NaCl co-transporter:
 - ⇒ the target of thiazide diuretics
 - ⇒ it contributes to the reabsorption of about 10% of the filtered load of sodium.
- Potassium is lost as a result of more sodium reaching the collecting ducts.
- Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload.
- The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

Bendroflumethiazide - mechanism of Hypokalemia:

- ↑ sodium reaching the collecting ducts
- Activation of the renin-angiotensin-aldosterone

Common adverse effects

- dehydration
- postural hypotension
- hyponatraemia, hypokalaemia, Hypomagnesaemia, hypercalcaemia
- aout
- impaired glucose tolerance
- impotence

Rare adverse effects

- thrombocytopaenia
- agranulocytosis
- · photosensitivity rash
- pancreatitis
- hypochloraemic alkalosis

Amiloride

- The potassium-sparing diuretic amiloride inhibits sodium channels in the distal segment
 of the distal convoluted tubule
- Amiloride →inhibits the action of aldosterone on the distal convoluted tubule producing potassium reabsorption.
- In treating a patient with congestive heart failure who develops hypokalaemia, the best choice is to add a small dose of amiloride to his furosemide therapy

Triamterene

- Triamterene, a potassium sparing diuretic similar to amiloride.
- occasionally prescribed with thiazide or loop diuretics, to prevent hypokalaemia.
- It inhibits the movement of sodium through channels towards the end of the distal tubule
 and collecting ducts, preventing the passage of sodium from the urinary space into the
 tubular cells. This action causes hyperpolarisation of the apical plasma membrane,
 preventing the secretion of potassium into the collecting ducts.
- Hyperkalaemia is common (>5%), and is unaffected by concurrent potassium depleting diuretics.
- In mild hyperkalaemia, (eg: K = 5.9 mmol/l) with no evidence of cardiac toxicity. The
 management involves stopping the triamterene, and repeating the U&E in one week.

Spironolactone

- Spironolactone is an aldosterone antagonist
- acts in the cortical distal convoluted tubule and collecting duct.

Indications

- ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- hypertension: used in some patients as a NICE 'step 4' treatment
- heart failure (see RALES study below)
- nephrotic syndrome
- Conn's syndrome
- **Spironolactone** is a diuretic with **anti-androgen effects**. This makes it a useful agent in the treatment of hormonal acne and hirsutism.
 - It blocks the androgen receptor and 5α-reductase enzyme that is responsible for the synthesis of dihydrotestosterone (DHT) and can be used to treat hirsutism.

Adverse effects

- hyperkalaemia
- gynaecomastia
 - ⇒ Spironolactone and **eplerenone** are both aldosterone receptor antagonists that have shown survival benefit in patients with NYHA III/IV systolic heart failure.

⇒ Eplerenone has a lower antiandrogenic effect compared to spironolactone and may, therefore, be preferable if patient develops erectile dysfunction and bilateral gynecomastia.

RALES

- NYHA III + IV, patients already taking ACE inhibitor
- low dose spironolactone reduces all-cause mortality

Eplerenone

Indications

 Eplerenone is a spironolactone-like agent indicated as an add-on to standard therapy after a myocardial infarction, and heart failure

Side-effects

- Common side-effects: hyperkalaemia, dizziness, hypotension, diarrhoea, nausea and prerenal renal dysfunction
- Uncommon side-effects: eosinophilia, dehydration, hypercholesterolemia and hypertriglyceridaemia

Cautions

 The drug is metabolised via the CYP3A4 system, so that inducers or inhibitors of the 3A4 enzyme subtype may precipitate drug interactions

Diuretic abuse

- Diuretic abuse is not uncommon amongst athletes and jockeys as a means of weight loss.
- The patient has a hypokalaemic alkalosis, and urine potassium excretion is high despite the hypokalaemia.

Respiratory drugs

Theophylline

- Theophylline, like caffeine, is one of the naturally occurring methylxanthines.
- The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD

Action

- The exact mechanism of action has yet to be discovered.
- One theory suggests theophyllines may be a non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP.
- antagonism of adenosine and prostaglandin inhibition
 - > It blocks the adenosine receptor
 - Blockade of the receptors by the ophylline results in:
 - relaxation of smooth muscles, especially bronchial muscles
 - constriction of cerebral blood vessels
 - stimulation of the cardiac pacemaker
 - stimulation of gastric secretions
- Theophylline also releases calcium ions from the sarcoplasmic reticulum in skeletal and cardiac muscle, thus enhancing their contractility, including diaphragmatic contractility
- plasma theophylline concentration of between 10 and 20 mg/l is required for satisfactory bronchodilatation.

Side effect

- At the rapeutic doses, the side-effect of Aminophylline \Rightarrow Jitteriness

- adverse effects can occur within the range 10-20 mg/l and both the frequency
- severity increase at concentrations above 20 mg/l

Factors increasing the plasma theophylline concentration:

- · heart failure
- cirrhosis
- viral infections
- increased age (the elderly)
- Diet:
 - Obesity
 - > High carbohydrate intake
 - ➤ High methylxanthine intake (for example, tea, coffee)
- drugs that inhibit its metabolism
 - ⇒ Commonly prescribed drugs that can increase serum theophylline levels include:
 - clarithromycin, erythromycin
 - ciprofloxacin,
 - cimetidine.
 - oral contraceptives
 - allopurinol.
 - Fluvoxamine
 - ⇒ Consideration should be given to reducing theophylline dose when these drugs are prescribed.
- · cessation of enzyme-inducing drugs.

Factors decreasing the plasma theophylline concentration: (increasing theophylline clearance):

- Diet:
 - ⇒ Low carbohydrate
 - ⇒ High protein intake
- Social:
 - ⇒ chronic alcoholism without cirrhosis
 - ⇒ smoking
 - Smoking cessation → sudden increase in the ophylline level
 - Regular tobacco use up-regulates hepatic enzyme activity; cessation will be associated with a decrease of hepatic enzyme activity, such that theophylline concentrations may increase.
- Drugs: drugs that induce liver metabolism: eg:
 - > Rifampicin
 - Carbamazepine.

Theophylline poisoning

- Theophylline has a narrow therapeutic window and needs close monitoring of its serum level to avoid toxicity
- Symptoms of toxicity may be delayed following the ingestion of sustained-release preparations for up to 48 h
- Theophylline toxicity occurs with concomitant use of clarithromycin due to inhibition of cytochrome P450 (CYP1A2 and CYP3A4) by clarithromycin.
- Features of mild to moderate theophylline toxicity include nausea, vomiting, epigastric, tremor, tachycardia, restlessness and hallucinations. Severe toxicity can cause convulsions, arrhythmias and metabolic acidosis.
- Studies have shown an approximate 20% increase in both peak and trough theophylline levels with concomitant use of clarithromycin and it is recommended that theophylline levels should be monitored prior, during and on cessation of clarithromycin and dosage

adjustment of theophylline made accordingly.

Features

- > mild to moderate theophylline toxicity
 - nausea, vomiting, epigastric,
 - tremor,
 - tachycardia,
 - restlessness and
 - hallucinations.
- Severe toxicity:
 - convulsions,
 - arrhythmias
 - metabolic acidosis, hypokalaemia and hyperglycaemia

Management

- > activated charcoal
- > charcoal haemoperfusion is preferable to haemodialysis

In cases of severe theophylline toxicity, charcoal haemoperfusion can be used

Antimuscarinic agent

- Muscarinic antagonists (antimuscarinic agents) are a group of anticholinergic drugs that competitively inhibit postganglionic muscarinic receptors.
- Which organ systems are most affected by an antimuscarinic agent depends on the specific characteristics of the agent, particularly its lipophilicity.
 - Lipophilic agents (i.e., atropine or benztropine) are able to cross the bloodbrain barrier and therefore affect the central nervous system (CNS) in addition to other organ systems.
 - Less lipophilic agents (i.e., ipratropium or butylscopolamine) are administered if the CNS does not need to be targeted, specifically for respiratory (e.g., asthma), gastrointestinal (e.g., irritable bowel syndrome), or genitourinary applications (e.g., urinary incontinence).

Action

 Muscarinic antagonists (the majority of anticholinergic drugs) inhibit the effect of acetylcholine on muscarinic receptors,

Effects of muscarinic antagonists

	scarinic antagonis			
Muscarinic receptors	Organ/Tissue	Effects		
M1, M4, M5	Central nervous system	 Influences neurologic function (e.g., cognitive impairment) 		
M2	Heart	 ↑ Heart rate Increases AV-node conduction → arrhythmias 		
МЗ	Smooth muscle	Gastrointestinal tract		
	Exocrine glands	↓ Secretions (sweat)		

Antimuscarinic side effects

"Blind as a bat (mydriasis), mad as a hatter (delirium), red as a beet (flushing), hot as a hare (hyperthermia), dry as a bone (decreased secretions and dry skin), the bowel and bladder lose their tone (urinary retention and paralytic ileus), and the heart runs alone (tachycardia)."

	Side effect	Contraindications
Impaired secretion by exocrine glands	 Dry mouth and sore throat ↓ Respiratory tract secretions Hyperthermia und warm, dry skin 	Acute asthma Respiratory distress
Cardiovascular system	Tachycardia	TachyarrhythmiasHeart failureMyocardial infarctionHyperthyroidism
Decreased smooth muscle tone	 Gastroesophageal reflux Obstipation or ileus Impaired micturition/urinary retention Vasodilatation and flush 	Hiatal hernia associated with reflux esophagitis Ulcerative colitis Paralytic ileus Obstructive disease of the gastrointestinal tract (e.g., achalasia, pylori c stenosis or duodenal stenosis) Obstructive uropathy (e.g., benign prostatic hyperplasia, urinary retention)
Eye	Mydriasis and photophobiaBlurred vision	Narrow- angle glaucoma
CNS	 Excitement, agitation, and hallucinations with the use of lipophilic parasympatholytics (e.g., atropi ne), especially in elderly patients Confusion, disorientation Coma, seizure, and rarely death 	Myasthenia gravis

Lipophilic antimuscarinic (good oral bioavailability and CNS penetration) (Tertiary amines)

Drug	od oral bioavailability and CNS Effect	Indication
Atropine	↑ Heart rate ↓ Secretions of exocrine glands ↓ Tone and motility of smooth muscles ↓Cholinergic overactivity in CNS Mydriasis and cycloplegia	First drug of choice in unstable (symptomatic) sinus bradycardia (IV) Premedication: prior to intubation to decrease salivary, respiratory, and gastric secretions Ophthalmology: uveitis Antidote for anticholinesterase poisoning Scorpion stings
Scopolamine(hyoscine)	Vestibular disturbances (antiemetic)	Motion sickness
Homatropine Tropicamide	Mydriasis Impair accommodation	Ophthalmology Therapeutic use: in patients with uveitis Diagnostic use: pupillary dilation to allow ocular fundus examination and cycloplegia to allow refractory testing
BenztropineBiperidenTrihexyphenidyl	↓ Cholinergic overactivity in CNS	 Antiparkisonian effect (Parkinson disease) Extrapyramidal symptoms (EPS) caused by antipsychotics
OxybutyninTolterodineSolifenacinDicyclomine	↓ Tone and motility of smooth muscle cells	Oxybutynin, tolterodine, and solifenacin: overactive bladder incontinence Dicyclomine: irritable bowel syndrome
Darifenacin	↑ Sphincter tone	Urinary urgency, urge incontinence, urinary frequency, and/or nocturia(symptoms resulting from, e.g., overactive bladder)

Hydrophilic (poor oral bioavailability and CNS penetration) (Quarternary amines)

Drug	Effect	Indication
Glycopyrrolate	Decreases secretions of exocrine glands	Peptic ulcer disease treatment
Ipratropium bromide Tiotropium bromide	Bronchodilation	COPD and bronchial asthma Ipratropium bromide: COPD grade I and higher Acute management of refractory asthma Tiotropium bromide: Longer duration of action Long-term treatment of COPD (grade II and above)

Anticholinergic syndrome (overdose)

- Etiology
 - > Belladonna poisoning
 - > Jimson weed/Angel's trumpet (Datura stramonium) poisoning
 - Medications
 - Anticholinergic agents (e.g., atropine, benztropine, trihexyphenidyl)
 - Drugs with anticholinergic properties
 - Tricyclic antidepressives (predominantly doxepin, amitriptyline, imipramine, and trimipramine)
 - Antipsychotics (e.g., clozapine, quetiapine)
 - First-generation antihistamines (e.g., promethazine, dimenhydrinate)
- Clinical features
 - Dry mouth, warm, flushed skin, thirst, tachycardia, arrhythmias, mydriasis, confusion, and agitation
 - Possibly anticholinergic delirium: Excessive use of tricyclic antidepressants (or other medications with significant anticholinergic effects) can cause lifethreatening delirium, hallucinations, and psychomotor symptoms.
- Treatment: antidote for purely anticholinergic poisoning (e.g. atropine): physostigmine

One mnemonic used to remember the symptoms of anticholinergic toxicity is:

Hot as a hare: increased body temperature Blind as a bat: mydriasis (dilated pupils)

Dry as a bone: dry mouth, dry eyes, decreased sweat

Red as a beet: flushed face Mad as a hatter: delirium

Tiotropium

Indications

 Tiotropium is a specific long-acting antimuscarinic agent indicated as maintenance therapy for patients with (COPD)

Cautions

 Caution is advised in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction

Side-effects

- Dry mouth
- Paradoxical bronchospasm
- Rarer side-effects include tachycardia, blurred vision, urinary retention and constipation

Doxapram

Indications

- Doxapram is a centrally acting respiratory stimulant, used in patients with severe respiratory disease who are deemed unsuitable for admission to the Intensive Therapy Unit
- Intravenous doxapram only used if the patient is not suitable for either intubation or noninvasive ventilation.
- The main purpose in using doxapram is to allow time for recovery from an acute respiratory event
- The usual dosing regimen is 1-4 mg/min given as an intravenous infusion

Contraindications

- · heart disease,
- epilepsy, cerebral oedema, stroke,
- · status asthmaticus,
- hypertension, hyperthyroidism and phaeochromocytoma

Side-effects

- hypertension,
- exacerbation of apparent dyspnoea,
- agitation,
- confusion,
- · sweating,

- cough,
- headache,
- dizziness,
- nausea, vomiting
- · urinary retention

Sodium cromoglicate

- Sodium cromoglicate principally acts by reducing the degranulation of mast cells triggered by the interaction of antigen and IgE
- The inhibitory effect on mast cells appears to be cell-type specific, since cromoglicate
 has little inhibitory effect on mediator release from human basophils
- More recent research has also shown that cromoglicate may act on eosinophils to reduce their inflammatory response to inhaled allergens, but this is not the most probable mechanism of action of sodium cromoglicate in the prophylaxis of asthma

Magnesium treatment in asthma

 Intravenous magnesium (1.2 - 2 g given over 20 minutes) is now indicated in the management of severe life threatening acute asthma attacks

Its principal actions are to:

• inhibit acetylcholine release at the neuromuscular junction

relax bronchial smooth muscle

stabilise mast cells

Unwanted effects are uncommon following single-dose therapy, although a slight decrease in blood pressure can be noticed and flushing can occur

Symptoms of hypermagnesaemia include:

- nausea
- confusion
- diarrhoea
- coma
- flushing
- loss of tendon reflexes
- hypertension

CNS & Psychiatric drugs

Anti-convulsants

Remarkable side effects of anti-epileptic drugs are:

- SIADH and rash (carbamazepine)
- Liver toxicity (sodium valproate)
- Severe rash (lamotrigine)
- Retinal damage (vigabatrin)
- · Aplastic anaemia (felbamate).
- Topiramate
 - ⇒ anticonvulsant ,most frequently prescribed for the prevention of migraines
 - ⇒ Side effects:
 - Renal stones
 - topiramate causes systemic metabolic acidosis, lowers urinary citrate excretion, and increases urinary pH. These changes increase the propensity to form calcium phosphate stones.
 - weight loss (weight gain with sodium valproate),
 - impaired taste sensation,
 - cognitive dysfunction
 - depression.
 - Tingling in extremities.

Felbamate

⇒ Because of its potentially fatal toxic effects (especially aplastic anemia and hepatic failure), the use of felbamate should be restricted to patients with severe partial epilepsy or Lennox-Gastaut syndrome who do not respond to other medications.

Lamotrigine

- ⇒ Lamotrigine has a black box warning because of its association with Stevens-Johnson syndrome.
 - the risk of tevens-Johnson syndrome increases if it is co-administered with valproate.
 - When co-administered with valproate, the dosage of lamotrigine should be half that required in the absence of valproate and should be very slowly escalated.

Epilepsy medication in pregnancy

- There is an increased risk of neural tube defects associated with anti-convulsants during pregnancy.
- However, the risks associated with treatment are outweighed by the benefits in preventing seizures, so the drug should be continued.
- The risks may be minimised through use of folate supplements.
- If a patient is planning on pregnancy, then registry studies suggest that lamotrigine would be the best choice
- Percentage of Congenital malformations associated with Anti-epileptics
 - ⇒ Valproate → 6% (neural tube defects in the fetus)
 - Valproate should be avoided in pregnancy if possible
 - NICE guidance suggests that phenytoin should be avoided in women of child-bearing age because of the risk of congenital malformations.
 - \Rightarrow Topiramate \rightarrow 4.3%
 - \Rightarrow Phenytoin \rightarrow 3.5% (fetal hydantoin syndrome with facial dysmorphism)
 - \Rightarrow Carbamazepine \rightarrow 2.5%
 - ⇒ General population →1.5%
 - ⇒ Primidone and phenobarbital → withdrawal symptoms in the newborn

Breast feeding is acceptable with nearly all anti-epileptic drugs

Contraception in epilepsy

- Phenytoin induces liver enzymes, thereby increasing oestrogen breakdown and reducing the effectiveness of oestrogen-containing contraceptives
- Where the combined contraceptive pill is used in conjunction with phenytoin, the contraceptive should contain high dose oestrogen: 50 mg ethinylestradiol or more
- Lamotrigine is a suitable first-line treatment for partial epilepsy, and does not alter oestrogen metabolism
- lamotrigine is the most appropriate choice in women of child-bearing age because:
 - ⇒ low risk of congenital malformations.
 - ⇒ it does not affect the effectiveness of the oral contraceptive pill
- Women taking lamotrigine monotherapy and oestrogen-containing contraceptives should be informed of the potential increase in seizures due to a fall in the levels of lamotrigine.
- Whilst Carbamazepine is a potent enzyme inducer and therefore can't be used in combination with the pill

Antiepileptic and weight (medical-masterclass.com 2017 part 2)

- Two antiepileptic medications have been found to <u>induce weight loss</u>; topiramate and zonisamide.
- Valproate, vigabatrin, gabapentin, carbamazepine, and pregabalin induce weight gain.
- Levetiracetam, lamotrigine, and phenytoin are weight neutral.

Sodium valproate

Indications

- management of epilepsy and is first line therapy for generalised seizures.
- acute mania

Action

- blockage of voltage-gated sodium channels
- increasing GABA activity (by inhibits GABA transaminase).

Adverse effects

- · gastrointestinal: nausea
- increased appetite and weight gain
- alopecia: regrowth may be curly (note that phenytoin → hirsutism while valporate → alopecia)
- ataxia
- tremor

- hepatitis
- pancreatitis
- thromobcytopaenia
- teratogenic
- hyponatraemia
- polycystic ovarian (PCOS) syndrome
- · strong inhibitor of CYP450s.

Which enzyme does Valproic Acid inhibit? GABA Transaminase

What ion channel does valproic acid block? voltage-gated sodium channels

Sodium valproate can lead to severe hepatic toxicity. more commonly if the patient has a metabolic or degenerative disorder, organic brain disease or severe seizures associated with mental retardation. Usually this reaction occurs within the first three months of therapy.

Phenytoin

Indications

- management of seizures.
- used as an antidote for Digitalis-induced arrhythmias.

Action

- blockage of voltage gated Na+ channels.
- refractory period of voltage-gated Na+ channels decreasing the sodium influx into neurons which in turn decreases excitability

Side effects

- Acute
 - initially: dizziness, diplopia, nystagmus, slurred speech, ataxia
 - later: confusion, seizures
- Chronic
 - common: gingival hyperplasia (secondary to increased expression of platelet derived growth factor, PDGF), hirsutism, coarsening of facial features, drowsiness
 - > megaloblastic anaemia (secondary to altered folate metabolism)

- > peripheral neuropathy
- > enhanced vitamin D metabolism causing osteomalacia
- lymphadenopathy
- dyskinesia

Idiosyncratic

- fever
- rashes, including severe reactions such as toxic epidermal necrolysis
- hepatitis
- Dupuytren's contracture (although not listed in the BNF)
- aplastic anaemia
- drug-induced lupus
- Hypocalcaemia
- Pseudolymphoma or, rarely, malignant lymphoma and mycosis-fungoides-like lesions.

Teratogenic

associated with cleft palate and congenital heart disease

Interaction

- Phenytoin would speed up metabolism of ethinyloestradiol making the pill less effective.
 - strong inducer of CYP450 enzymes.
- Cimetidine increases the efficacy of phenytoin by reducing its hepatic metabolism
- Sucralfate may decrease the pharmacological effects of phenytoin when administered concurrently
- Effect on other anti-epileptic:
 - ⇒ Phenytoin usually lowers the serum concentration of carbamazepine, clonazepam, topiramate and sodium valproate.
 - **⇒** elevates the serum level of phenobarbitone.
 - ⇒ Phenytoin does not appear to influence the serum concentration of levetiracetam.

In renal failure

Renal failure $\Rightarrow \downarrow$ drug affinity for protein binding $\Rightarrow \uparrow$ free drug \Rightarrow toxicity (drug level may be within the therapeutic range)

- In patients with renal failure, dose reduction of phenytoin is therefore required.
- Other drugs where this may be a problem include sodium valproate and warfarin.

There is no oral preparation of <u>fosphenytoin</u>; it is used in status epilepticus only.

<u>Phenytoin toxicity</u> typically gives rise to a cerebellar-like syndrome. Nystagmus is present even in mild toxicity.

Carbamazepine

Carbamazepine is chemically similar to the tricyclic antidepressant drugs.

Indications:

- most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication.
- Other uses include
 - neuropathic pain (e.g. trigeminal neuralgia, diabetic neuropathy)
 - bipolar disorder

Mechanism of action

binds to sodium channels increases their refractory period

Adverse effects

- P450 enzyme inducer
 - ➤ Auto-induction of carbamazepine metabolism → need to increase the dose to achieve a therapeutic plasma concentration.
 - ➤ In patients on carbamazepine who develop Hashimoto's thyroiditis the dose of thyroxine should be increased to maintain therapeutic levels
- dizziness and ataxia
- drowsiness
- headache
- nystagmus
- visual disturbances (especially diplopia)
 - The most common dose-related adverse effects of carbamazepine are diplopia and ataxia
- Steven-Johnson syndrome
 - ➤ HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine.
 - > The prevalence of the HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations.
 - Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine
- leucopenia and agranulocytosis
- syndrome of inappropriate ADH secretion
- Carbamazepine is nephrotoxic and may cause proteinuria.

Carbamazepine overdose presents with:

- Drowsiness
- Tremor
- Slurred speech
- · Blurred vision

Ataxia

- Seizures
- Hallucinations
- · Oliguria, and

Nausea

· Bullous skin lesions.

Vomiting

Contraindications:

- atrioventricular (AV) conduction abnormalities
- porphyria
- history of bone marrow depression

Vigabatrin

Vigabatrin → Visual field defects

Action

• Inhibition of GABA Transaminase, thereby increasing GABA levels

Indication:

- Vigabatrin should be used only in combination with other anti-epileptic drugs for patients with resistant partial epilepsy when all other appropriate drug combinations have proved inadequate or have not been tolerated.
- Vigabatrin is the drug of choice for infantile spasms, is not generally used outside the situation of infantile spasms

Adverse effects:

- · reduced peripheral vision
 - ⇒ 40% of patients develop visual field defects, which may be irreversible
 - ⇒ The pattern of the field defect is typically a bilateral, absolute concentric constriction of the visual field, the severity of which varies from mild to severe.
 - ⇒ Vigabatrin-associated field defects are typically nasal more so than temporal,
 - ⇒ visual fields should be checked before the start of treatment and every 6 months
- aggression
- alopecia
- retinal atrophy

Topiramate

a patient with epilepsy and hepatic impairment -> Topiramate

- Action
 - ⇒ blocks voltage-gated Na+ channels
 - ⇒ ↑ GABA action
- advantages
 - ⇒ Topiramate is one of the few antiepileptic drugs (also including gabapentin) with almost exclusively renal metabolism
 - ⇒ It would be less likely to cause worsening of hepatic function
- adverse effects of topiramate include
 - > renal stones
 - weight loss
 - > and neuropsychiatric side-effects

<u>Gabapentin</u>

- MOA of Gabapentin and Pregabalin?
 - Inhibits voltage gated Ca channels as a GABA analog
- **used for add-on therapy** in partial or generalised seizures.
- does not induce cytochrome P450 unlike other anticonvulsants such as phenytoin and phenobarbitone.
- · Requires dose adjustment in renal disease

Levetiracetam (Keppra)

- Action
 - unknown.
- it does not affect hepatic enzymes, but dose reduction is required in renal failure.
- Usage:
 - Is an adjunctive treatment for partial seizures with or without secondary generalisation.
- Advantages:
 - The drug appears to be well tolerated with few side effects.
 - > has least interactions and is safe with warfarin.

Procyclidine

- Action
 - > antimuscarinic
- Indication
 - used to treat the Parkinsonian side effects of neuroleptics;
- Signs of procyclidine overdose include:
 - Agitation
 - Confusion
 - > Sleeplessness lasting up to 24 hours or more
 - > Pupils are dilated and unreactive to light.
 - Visual and auditory hallucinations and tachycardia have also been reported.

Barbiturates

- Examples
 - phenobarbital, pentobarbital, thiopental, and secobarbital
- Mechanism
 - increases GABA_A action by ↑ duration of Cl⁻ channel opening resulting in ↓ neuron firing
 - barbitDURATE
- Clinical use
 - > CNS depressant for anxiety and seizures
 - > induction of anesthesia (thiopental)
- kinetics
 - > induction of P450
 - > tolerance/dependence
- Phenobarbitone suppress the central nervous system causing:
 - Hypoventilation (and therefore a respiratory acidosis)
 - Hypotension, and
 - Hypothermia.

Anticholinergic syndrome

Common causes	Signs and symptoms	Management
 tricyclic antidepressants 	hot, dry skin	supportive
 atropine 	 hypertension 	
 H-1-antihistamines 	tachycardia	
	urinary retention	
	dilated pupils (mydriasis)	
	Agitated delirium can also occur	

- Although physostigmine, a reversible inhibitor of acteylcholinesterase, is effective in treating symptoms, there is a significant risk of cardiac toxicity (bradycardia, AV conduction defects and asystole).
- Treatment therefore consists of withdrawal of the precipitating drug and supportive care.

Serotonin syndrome

Causes

- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines
- The serotonin syndrome occurs primarily because of interactions between monoamineoxidase inhibitors (MAOI) and drugs that enhance serotonin function (eg selective serotonin-reuptake inhibitors (SSRIs))

Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, Tremor, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- · altered mental state
- sweating
- tachycardia

Management (Cyproheptadine may be useful in treatment)

- · stopping the precipitating drugs
- instituting generalised cooling measures and diazepam to reduce agitation
- Studies have suggested that drugs possessing serotonin-antagonist activity (eg cyproheptadine, methysergide) may provide some benefit in the management of patients with the serotonin syndrome

Oculogyric crisis

An oculogyric crisis is a dystonic reaction to certain drugs or medical conditions

Features

- · restlessness, agitation
- involuntary upward deviation of the eyes

Causes

- phenothiazines
- haloperidol
 - Usually a consequence of typical neuroleptic drugs such as haloperidol or chlorpromazine, but is unusual with newer agents such as olanzapine or clozapine.
- metoclopramide
- · postencephalitic Parkinson's disease

The condition is often precipitated by re-introduction of the agent.

Management

- procyclidine (usually IV or IM)
- Benztropine

St John's Wort

Overview

- shown to be as effective as tricyclic antidepressants in the treatment of mild-moderate depression
- mechanism: thought to be similar to SSRIs (although noradrenaline uptake inhibition has also been demonstrated)
- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be
 prescribed or advised because of uncertainty about appropriate doses, variation in the
 nature of preparations, and potential serious interactions with other drugs'

Adverse effects

- · profile in trials similar to placebo
- can cause serotonin syndrome
- **inducer of P450 system**, therefore decreased levels of drugs such as warfarin, ciclosporin. The effectiveness of the combined oral contraceptive pill may also be reduced.

Dopamine receptor agonists

Overview

- e.g. bromocriptine, cabergoline, ropinirole, apomorphine
- ergot-derived dopamine receptor agonists (<u>bromocriptine</u>, <u>cabergoline</u>, pergolide*) have been associated with pulmonary, retroperitoneal and cardiac **fibrosis**.
 - ⇒ The Committee on Safety of Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
 - ⇒ *pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

Action

- L-DOPA is a precursor of dopamine. Dopamine itself does not cross the blood-brain barrier and so is no effective as a drug.
- Levodopa exerts its therapeutic action after being converted by dopa decarboxylase to dopamine in the brain (in the striatum).
- It is also converted to dopamine in the periphery, causing nausea and vomiting through action at the area postrema, which lies outside the blood-brain barrier in the brain stem.

Indications

- · Parkinson's disease
 - ⇒ Currently treatment is delayed until the onset of disabling symptoms
 - ⇒ If the patient is elderly, L-dopa is sometimes used as an initial treatment
- prolactinoma/ galactorrhoea
- · cyclical breast disease
- acromegaly

Adverse effects

- nausea/vomiting
- postural hypotension
- hallucinations
- · daytime somnolence

Bromocriptine

Action

• Bromocriptine is an ergotamine dopamine agonist that leads to activate <u>central and peripheral</u> D2 receptors

Indications

- used to inhibit prolactin release from the anterior pituitary
- preferred in women who are looking to get pregnant (less teratogenicity than cabergoline).

Side effects

- Common: nausea, nasal congestion, constipation,
- **Uncommon:** dizziness (orthostatic hypotension)
- Rare
 - **⇒** Tinnitus
 - ⇒ Excessive sleepiness (it is seen more commonly with modern agents such as ropinirole).
 - ⇒ Pulmonary fibrosis
 - ⇒ Vasospasm in the peripheral circulation: Higher doses may cause cold-induced peripheral digital vasospasm (Raynaud's phenomenon).
 - ⇒ Hallucinations and psychosis: exacerbation or unmasking of depression and psychosis (only at very high doses)

Dopa-decarboxylase inhibitors

- Reduce the extracerebral complications of L-dopa therapy. These include nausea, vomiting, postural hypotension and cardiac arrhythmias.
- When given in combination with dopamine agonists dyskinetic movements are more likely.
- Carbidopa is an inhibitor of dopa decarboxylase that does not cross the blood-brain barrier, so it
 reduces peripheral, but not central, metabolism of levodopa to dopamine, thereby reducing the
 unwanted side effect but not the therapeutic action.
- Benserazide is another peripheral dopa decarboxylase inhibitor that is commonly used in combination with levodopa (as co-beneldopa (Madopar)).

Amitriptyline (tricyclic antidepressants)

Adverse effects

Antimuscarinic effects: relatively common and occur before an antidepressant effect is obtained.

- Dry mouth
- Constipation → paralytic ileus
- Urinary retention

- Blurred vision and disturbances in accommodation
- · Increased intraocular pressure, and
- Hyperthermia.
- Tolerance is often achieved if treatment is continued
- adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Neurological adverse effects:

- Drowsiness
- Headache
- Peripheral neuropathy
- Tremor
- Ataxia
- Epileptiform seizures
- Tinnitus

 extrapyramidal symptoms including speech difficulties (dysarthria). Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Gastrointestinal complaints include:

- Sour or metallic taste
- Stomatitis, and
- · Gastric irritation with nausea and vomiting.
- · rarely, cholestatic jaundice

cardiovascular

 Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

blood disorders:

- Eosinophilia
- · Bone marrow depression
- Thrombocytopenia
- Leucopenia, and
- Agranulocytosis.

Endocrine effects

- · testicular enlargement
- gynaecomastia and breast enlargement, and galactorrhoea.
- Sexual dysfunction.
- Changes in blood sugar concentrations
- hyponatraemia associated with inappropriate secretion of antidiuretic hormone.
- increased appetite with weight gain (or occasionally anorexia with weight loss).
- Sweating may be a problem.

Others

 Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported

Tricyclic overdose

Tricyclic overdose - give IV bicarbonate

- Overdose of tricyclic antidepressants is a common presentation to emergency departments.
 Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose.
- Other tricyclic antidepressants includes imipramine
- Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- Hypertension
 - ⇒ results from the blockade of norepinephrine reuptake
 - ⇒ is an early and transient finding.
 - ⇒ Catecholamines are eventually depleted and in most patients hypertension is mild and self-limiting and is best left untreated.
- Orthostasis and hypotension
 - ⇒ are the result of direct myocardial depression, catecholamine depletion, alphaadrenergic blockade, and arrhythmias.
 - ⇒ The combination of decreased contractility and vasodilation produce decreased preload and can result in severe and refractory hypotension.
- Arrhythmias
 - secondary to blockage or slowing of fast sodium channels (causing a quinidine-like effect)
 - ⇒ the most serious consequence of TCA overdose.
 - Mild overdoses produce sinus tachycardia, mostly as a result of anticholinergic effects.
 - More severe overdoses result in prolonged QRS and QTc intervals, followed by a prolonged PR interval, and, finally, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation.
- seizures
- · metabolic acidosis
- coma

ECG changes include: (ECG is the most appropriate initial action)

- sinus tachycardia
- widening of QRS
- · prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

Management

- Check U&Es, looking specifically for hypokalaemia, and ABG looking for acidosis.
 Hypokalaemia should be corrected. ECG should be done to assess the QRS interval.
- Gastric lavage should only be considered if it is within one hour a potentially fatal overdose. 50 g of charcoal can be given if it is within one hour of ingestion.
- 50 ml of 8.4% sodium bicarbonate should be given if the pH is less than 7.1, QRS interval is more than 0.16 s, or there are cardiac arrhythmias or hypotension.

- Indication for sodium bicarbonate in tricyclic poisoning includes wide QRS complex.
- Intravenous sodium bicarbonate is the standard initial therapy for patients who develop cardiotoxicity (usually a QRS > 100ms or a ventricular arrhythmia) as a result of tricyclic antidepressant (TCA) overdose.
 - Mechanism of Sodium bicarbonate action:
 - alkalinisation of blood to a pH of 7.45-7.55 uncouples TCA from myocardial sodium channels;
 - also, additional sodium increases extracellular sodium concentration, thereby improving the gradient across the channel.
- Intravenous magnesium sulphate can be used as a second-line agent in refractory arrhythmias.
- > IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are
 contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should
 also be avoided as they prolong the QT interval. Response to lignocaine is variable and it
 should be emphasized that correction of acidosis is the first line in management of tricyclic
 induced arrhythmias
- · intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- · dialysis is ineffective in removing tricyclics
- Patients who display signs of toxicity should be monitored for a minimum of 12 hours.

Tricyclic Withdrawal symptoms rare and include:

- cholinergic effects such as: abdominal cramps, diarrhoea, vomiting and dehydration
- extrapyramidal symptoms such as: anxiety, psychosis, delirium and mania

Monoamine oxidase (MAO) inhibitors

Overview

· serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell

Non-selective monoamine oxidase inhibitors

- e.g. tranylcypromine, phenelzine
- used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder
- not used frequently due to side-effects
- Abrupt withdrawal of phenelzine leads to panic, shaking, sweats and nausea

Adverse effects of non-selective monoamine oxidase inhibitors

- hypertensive reactions with tyramine containing foods e.g. cheese, pickled herring, Bovril, Oxo, Marmite, broad beans
- · anticholinergic effects

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.

- citalopram and fluoxetine are currently the preferred SSRIs
- sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

Adverse effects

gastrointestinal symptoms are the most common side-effect

- there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- patients should be counselled to be vigilant (حنر) for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions
- The Committee on Safety of Medicines (CSM) have reported that hyponatraemia is
 associated with all types of antidepressants; however it has been reported more
 frequently with selective serotonin reuptake inhibitors (SSRIs) than with other
 antidepressants.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion or convulsions whilst taking an antidepressant.

Citalopram and the QT interval

- citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with:
 - congenital long QT syndrome;
 - known pre-existing QT interval prolongation;
 - > or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

Interactions

- NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine
- aspirin: see abovetriptans: avoid SSRIs
- monoamine oxidase inhibitor (MAOI)→ serotonin syndrome

follow up

- Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.
- For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.
- If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

Discontinuation symptoms

- When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine).
- Paroxetine has a higher incidence of discontinuation symptoms
 - Withdrawal of paroxetine can lead to deterioration in mood and cognition and orofacial dystonias
- Symptoms:
- increased mood change
- restlessness
- difficulty sleeping
- unsteadiness

- sweating
- gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- paraesthesia

Lithium

Lithium: fine tremor in chronic treatment, coarse tremor in acute toxicity

- Lithium is mood stabilising drug used most commonly prophylactically in <u>bipolar disorder</u> but also as an adjunct in refractory depression.
- It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys.

Mechanism of action - not fully understood, two theories:

- interferes with inositol triphosphate formation
- interferes with cAMP formation

Adverse effects

Chronic lithium use is recognised to reduce both cAMP- and non-cAMP-related upregulation of *aquaporin-2* gene expression. The role of aquaporin-2 is to drive reuptake of water from the urine, and the number of aquaporin-2 channels is increased in response to vasopressin. Blockade of the upregulation of *aquaporin-2* gene expression reduces the effect of vasopressin causing nephrogenic diabetes insipidus.

- · nausea/vomiting, diarrhoea
- fine tremor
- polyuria (secondary to nephrogenic diabetes insipidus)
- thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- · weight gain
- Hypercalcaemia and primary hyperparathyroidism.
 - ⇒ It has been suggested that lithium → alters the sensitivity of the parathyroid cells to calcium → hyperplasia.
 - Other studies have however failed to confirm an excess of parathyroid hyperplasia in this population, suggesting instead that lithium selectively stimulates growth of parathyroid adenomas in susceptible patients, who are best treated therefore with adenoma excision rather than total parathyroidectomy.

Pregnancy

- Exposure to lithium in utero is associated with Ebstein's anomaly.
- Lithium is contraindicated during the first trimester and when breast-feeding.
- In the first trimester lithium can cause atrialisation of the right ventricle.
- During the second and third trimesters lithium can be used, but dose requirements are increased.
- Immediately after delivery lithium dose requirements return to normal abruptly. Lithium levels can rise dangerously if a high dose is continued.
- Long-term treatment with lithium can produce frank hypothyroidism
 - Lithium is concentrated by the thyroid and inhibits thyroidal iodine uptake. It also inhibits iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion.
 - The best management in this case would be to discontinue the lithium therapy and replace it with another agent (after consulting the patient's psychiatrist) carbamazepine, sodium valproate or lamotrigine could all be alternative agents for mood stabilisation. Lamotrigine is the preferred option, assuming pregnancy is

desired.

 Lithium is excreted in breast milk and if the infant becomes dehydrated, then toxic lithium levels develop rapidly.

Monitoring of patients on lithium therapy

- NICE and the National Patient Safety Agency (NPSA) recommends:
 - lithium blood level should 'normally' be checked every 3 months. Levels should be taken 12 hours post-dose
 - thyroid and renal function should be checked before starting treatment and then every 6 months
 - 3. patients should be issued with an information booklet, alert card and record book
 - 4. monitor serum lithium levels 1 week after treatment starts and every dose change, and then every 3 months.

Lithium monitoring (NICE 2017):

thyroid and renal function	serum lithium levels	ECG
before treatment	1 week after treatment starts	For people at high risk of cardiovascular disease
every 6 months	every dose change	
	every 3 months	

Sodium valproate is the second line therapy for bipolar disorder in patients who don't tolerate lithium or where it's contraindicated.

Interaction:

- Acetazolamide leads to decreased lithium concentration
 - ⇒ Osmotic diuretics and carbonic anhydrase inhibitors such as acetazolamide lead to decreased lithium concentration because of increased excretion
- Calcium channel blockers combined with lithium may cause a syndrome of ataxia, confusion and sleepiness, which is reversible on stopping the drug.
- ACE inhibitors lead to increased lithium concentration because of decreased excretion.
- thiazide diuretics increased lithium reabsorption and may cause lithium intoxication.
- Methyldopa also leads to increased risk of neurotoxicity.

Lithium toxicity

Toxicity may be precipitated by dehydration, renal failure, diuretics (Especially bendroflumethiazide) or ACE inhibitors and ARBs

- Lithium has a very narrow therapeutic range (0.4-1.0 mmol/L)
- long plasma half-life (20 h)
- · excreted primarily by the kidneys.
- Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.
- Toxicity may be precipitated by dehydration, electrolyte imbalance, renal failure, , and drugs

Drugs that may precipitate lithium toxicity include:

- diuretics (especially bendroflumethiazide),
- ACE inhibitors & ARB
- NSAIDs
- Metronidazole
- Tetracycline

- Phenytoin
- Ciclosporin
- Methyldopa

Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- dysarthria
- ataxia
- seizure
- coma

Mild to moderate toxicity	severe toxicity
(levels less than 2 mmol/L)	(levels more than 2 mmol/L)
 anorexia 	 circulatory failure
 vomiting 	• coma
ataxia	 convulsions
 dysarthria 	 hyper-reflexia
 blurring of vision 	oliguria
 coarse tremor 	 psychosis, and
 diarrhoea 	 death (in severe cases).
 drowsiness, and 	
 muscle weakness. 	

Management

- The management of lithium toxicity is largely supportive.
- The first step is to establish renal function and correct serum electrolytes.
- Which investigation will help you in the immediate setting?
 - ⇒ Serum electrolytes and renal function
 - Renal function will determine the patient's ability to excrete lithium.
 - Lithium levels should be taken but may be of limited value in the acute setting (rapid result may not be available; levels not always reliable especially with sustained release preparations).
- mild-moderate toxicity may respond to volume resuscitation with normal saline.
 - In case of significant hypernatraemia, 5% dextrose is an initial option for fluid replacement
- · haemodialysis may be needed in severe toxicity
 - indication of Haemodialysis:
 - if serum lithium levels > 4 mmol/l or
 - serum lithium levels > 2.5 mmol/l with signs of significant lithium toxicity (e.g. seizures, depressed mental status) or inability to excrete lithium (e.g. renal disease, decompensated heart failure).
- sodium bicarbonate is sometimes used but there is limited evidence to support this.
 - > By increasing the alkalinity of the urine, it promotes lithium excretion
- Activated charcoal does not bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected.
- Whole bowel irrigation should be considered in adults who have ingested a <u>slow release</u> <u>preparation</u> of lithium of greater than 4 g.

Prognosis

10% of patients who survive severe lithium toxicity will be left with a neurological deficit.

Therapeutic drug monitoring

Lithium

- range = 0.4 1.0 mmol/l
- take 12 hrs post-dose

Digoxin

at least 6 hrs post-dose

Ciclosporin

trough levels immediately before dose

Phenytoin

· trough levels immediately before dose

Baclofen

- gamma-aminobutyric acid-B receptor agonist
- The primary site of action is the spinal cord by depressing monosynaptic and polysynaptic transmission.
- It can hyperpolarise cells by increasing K⁺ conductance and inhibit Ca²⁺ channels in others.
- Avoid abrupt withdrawal as it can cause serious side-effects including:
 - ⇒ Autonomic dysreflexia.
 - ⇒ hallucinations

Baclofen toxicity

- Onset of toxicity is rapid and its effect can last up to 35-40 hours post ingestion.
- · Features include:
 - Drowsiness
 - Coma
 - Respiratory depression
 - CO2 retention is likely to be due to central nervous system depression and reduction in diaphragmatic contraction secondary to baclofen toxicity.
 - Hyporeflexia
 - Hypotonia
 - Hypothermia, and
 - Hypotension.
 - Bradycardia with first degree heart block and prolongation of Q-T interval can occur.
- Treatment is usually supportive and often requires intensive care.
 - > Intubation and mechanical ventilation
- Patients with a high risk of aspiration pneumonia (↓ glasgow coma scale (GCS)) are a contraindication to non-invasive ventilation.

Endocrinology drugs

For all diabetic drugs → See endocrinology

lipid-lowering agents

See endocrinology (Hyperlipidaemia: management)

Octreotide

Octreotide

Stimulation of the somatostatin (SMS) receptor

Overview

- long-acting analogue of somatostatin
- somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin

Uses

- acute treatment of variceal haemorrhage
- acromegaly
- gastrinomas
- · carcinoid syndrome
- prevent complications following pancreatic surgery
- VIPomas
- · refractory diarrhoea

Adverse effects

• gallstones (secondary to biliary stasis)

Orlistat → Reduces fat absorption from the intestine

- Orlistat promotes weight loss and improves co-morbidities in obese patients
- Orlistat operates by preventing the absorption of fat molecules in the intestinal tract
- Approximately 30% of fat that would otherwise have been absorbed passes straight through the bowel and is excreted in the faeces
- As a result it can cause 'fatty stools', urgency and increased frequency of defaecation often with anal leakage or oily spotting
- these effects encourage people taking the drug to limit fat intake
- Orlistat itself is not absorbed, except in very small quantities and thus its side-effects are restricted to the gastrointestinal tract
- Patients taking orlistat may require concomitant vitamin supplements because of malabsorption of fat-soluble vitamins such as vitamins A, D, K and E
- Orlistat is shown to be clinically efficacious in reducing a person's weight over a period of a year
- Study results also showed significant improvement in reducing fasting glucose, total cholesterol, LDL-cholesterol and blood pressure

Obs & Gyna drugs

Prescribing in pregnant patients

Very few drugs are known to be completely safe in pregnancy. The list below largely comprises of those known to be harmful.

Drugs	Antibiotics
 ACE inhibitors, ARBs 	Tetracyclines
 Statins 	 Aminoglycosides
Warfarin	 Sulphonamides
 Sulfonylureas 	Trimethoprim
 Retinoids (including topical) 	 Quinolones: the BNF advises to avoid
Cytotoxic agents	due to arthropathy in some animal
	studies

- The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk.
- Verapamil is relatively safe in pregnancy and has been widely used to treat maternal and fetal supraventricular tachycardias.
- Amiodarone is associated with fetal hypothyroidism,
- · lisinopril with oligohydramnios,
- lithium with Ebstein's anomaly,
- and warfarin with facial / CNS abnormalities.

Combined oral contraceptive pills

Mechanisms of action

- Estrogen
 - ⇒ Hypothalamus: ↓ release of GnRH
 - ⇒ Pituitary: ↓ LH → inhibits ovulation, ↓ FSH → prevents ovarian folliculogenesis
 - **Progestin** → thickens the cervical mucus, preventing the entry of sperm.

Advantages

- Treatment of menopausal symptoms such as hot flashes.
- Other beneficial effects of MHT include the decreased risk of colon cancer, diabetes mellitus type 2, and all-cause mortality for women ages 50-59 years.

Emergency contraception (after unprotected sexual intercourse)

- Most effective when taken within 3 days of intercourse
 - ⇒ The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours.
- Typically administered as a single dose or as two doses over one day
- · Significantly less effective in patients who are obese or overweight
- Action of emergency contraception:
 tubal motility and ciliary activity thereby preventing sperm from reaching the oocyte in the ampulla of the tube.
- Example: levonorgestrel

Side effects

- Irregular periods (unscheduled bleeding): is the most common adverse effect
- Breast tenderness
- Headaches
- ↑ incidence of functional ovarian cysts, hepatic adenomas
- †relative risk of venous and arterial thrombotic events.
- Erythema nodosum

Transdermal administration of estradiol is associated with a lower risk of stroke and venous thromboembolism than oral administration of estradiol and is unlikely to increase the risk of stroke and venous thrombosis above that of non-users.

Contraindications

- People >35 years old who smoke tobacco (risk of cardiovascular events)
- Migraine (especially with aura)
- · Breast cancer
- Liver disease.
- breast feeding < 6 weeks post-partum
- Uncontrolled hypertension
- History of thromboembolic disease (stroke or ischaemic heart disease)

Progestogen only pills (POPs)

- Examples: Norethindrone, drospirenone, and desogestrel
- Mechanism of contraception:
 - ⇒ Norethindrone → thickening cervical mucus thereby preventing sperm penetration; ovulation is not consistently suppressed.
 - \Rightarrow Drospirenone and desogestrel \rightarrow suppression of ovulation.
- Advantages
 - ⇒ can be used whilst breast-feeding
 - ⇒ can be used in situations where the combined oral contraceptive pill is contraindicated (most women with medical comorbidities).
- Failure rate = over 7 % (women choosing POPs are often subfertile as a result of breastfeeding or older reproductive age)
- Hepatic enzyme-inducers (e.g. anticonvulsants phenytoin, carbamazepine, topiramate, and barbiturates and the antituberculosis drug rifampin) → Jefficacy of POPs.

Studies have shown that women taking estrogen- progestin combination OCPs before menopause have an increased risk of cervical carcinoma but a decreased risk of endometrial and ovarian carcinoma.

An entirely normal 16-year-old girl is very tall and would like to stop growing. What is the most appropriate treatment for her?

- → Oral contraceptive pill
 - The oral contraceptive pill used in this context would be associated with fusion of long-bone growth plates, and subsequent cessation of longitudinal growth.
 - Although ideally she should be encouraged not to receive medical intervention at all, in this situation use of the OCP represents the lowest-risk option.

What is the action of emergency contraception in preventing conception following unprotected sexual intercourse.?

Decreasing tubal motility and ciliary activity thereby preventing sperm from reaching the oocyte in the ampulla of the tube.

The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours after unprotected sexual intercourse. The earlier it is taken, the lower the likelihood of pregnancy!

Breakthrough bleeding is most commonly associated with low-dose combined oral contraceptive pills, especially those containing 20 micrograms ethinylestradiol.

Breast feeding: contraindications

Breast feeding is acceptable with nearly all anti-epileptic drugs

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- galactosaemia
- viral infections this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

SAFE **DANGEROUS** Antibiotics: ciprofloxacin, tetracycline, • Antibiotics: penicillins, cephalosporins, trimethoprim chloramphenicol, sulphonamides • Endocrine: glucocorticoids (avoid high doses), Psychiatric drugs: lithium, benzodiazepines, levothyroxine* clozapine Epilepsy: sodium valproate, carbamazepine Aspirin Asthma: salbutamol, theophyllines Carbimazole • Psychiatric drugs: tricyclic Sulphonylureas antidepressants, antipsychotics** Cytotoxic drugs Hypertension: β-blockers, hydralazine, Amiodarone methyldopa vitamin A derivatives. • Anticoagulants: warfarin, heparin

*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening

^{**}clozapine should be avoided

Drug causes teratogenesis
Some common drugs and their potential teratogenic effect are given below:

Come common drugs and their potential teratogenic effect are given below.		
drug	teratogenic effect	
Androgens	cardiac deformities	
Alcohol	fetal alcohol syndrome	
Carbamazepine	microcephaly	
Diethylstilbestrol	vaginal carcinoma	
Lithium	cretinism	
Phenobarbital	cleft palate	
Sodium valproate	neural tube defects	
Thalidomide	phocomelia	
Warfarin	chondrodysplasia punctata	

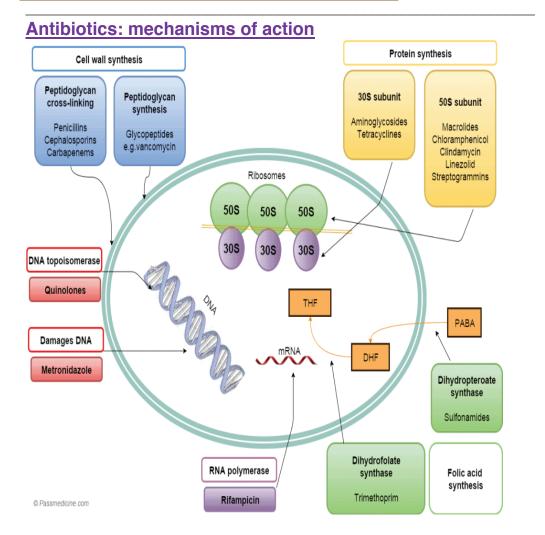
Unwanted drug effects in pregnancy

drug	effects in pregnancy
ACE inhibitors	oligohydramnios, impaired renal function
Aspirin	kernicterus
β-Blockers	hypoglycaemia, intrauterine growth retardation, fetal bradycardia
Carbimazole	neonatal goitre
NSAIDs	close ductus arteriosus
Sulphonamides	kernicterus
Thiazide diuretics:	neonatal thrombocytopenia

Antimicrobial

Antibiotics: bactericidal vs. bacteriostatic

Bactericidal antibiotics	Bacteriostatic antibiotics
 penicillins cephalosporins aminoglycosides nitrofurantoin metronidazole quinolones rifampicin isoniazid 	 chloramphenicol macrolides tetracyclines sulphonamides trimethoprim



The lists below summarise the site of action of the commonly used antibiotics

Inhibit cell wall formation	Inhibit protein synthesis (by acting on ribosome)	Inhibit DNA synthesis	Inhibit RNA synthesis
peptidoglycan cross-linking • β-lactams > Penicillins > Cephalosporins • carbopenems peptidoglycan synthesis glycopeptides Vancomycin teicoplanin Isoniazid (Those organisms lacking a cell wall are resistant to these drugs eg. Chlamydia's)	50S subunit 1. chloramphenicol 2. macrolides (e.g. erythromycin) 3. fusidic acid 4. (Quin/Dalfo)pristin 5. Linezolid 30S subunit 1. aminoglycosides (cause misreading of mRNA) 2. tetracyclines	quinolones (e.g. ciprofloxacin) Damages DNA 1. metronidazole Inhibits folic acid formation 1. sulphonamides 2. trimethoprim	•Rifampicin

Antibiotics: anaerobic activity

antibiotics have anti-anaerobic activity	antibiotics do not have anti-anaerobic activity
 penicillins cephalosporins (except ceftazidime) erythromycin metronidazole tetracycline 	gentamicinciprofloxacinceftazidime

Skin rash with antibiotics

- Ampicillin and amoxicillin can cause skin rashes that are **not allergic** in nature
- Erythromycin, benzylpenicillin, cefuroxime and cefadroxil all produce a diffuse, papular, non-purpuric rash that may be intensely pruritic
- A maculopapular rash is also seen when tonsillitis/pharyngitis is related to EBV infection

Cephalosporins

- Cephalosporins are safe inpenicillin allergy if it is only a rash.
- Only ceftazidime and cefepime will cover Pseudomonas

Co-trimoxazole

The sulfamethoxazole in co-trimoxazole causes haemolysis in G6PD, not the trimethoprim

Indications

- now only indicated for oral prophylaxis against Pneumocystis pneumonia, toxoplasmosis and nocardiosis
- It should only be considered in the treatment of chronic bronchitis or urinary tract infection where there is no other alternative

Side-effects

nausea, vomiting,

- allergy: rash (including Stephens-Johnson syndrome), toxic epidermal necrolysis and photosensitivity
- Blood disorders: neutropenia, thrombocytopenia and, rarely, agranulocytosis

Cautions/contraindications

• used with caution (or avoided) in renal or hepatic impairment

Aminoglycosides

Action

- bactericidal antibiotics that bind to the 30S ribosome and inhibit bacterial protein synthesis.
- active only against aerobic gram-negative bacilli and cocci.
 - ➢ ineffective against anaerobic bacteria as they require O₂ to enter bacterial cells.

Indications

- endocarditis in combination with penicillin (gentamycin)
- added to a beta-lactam antibiotic when serious Pseudomonas aeruginosa (cystic fibrosis)
- tuberculosis (streptomycin)

Side effects

- Nephrotoxicity
 - The reversible acute tubular necrosis after aminoglycoside reflects a concurrent impairment in the concentrating ability, and most patients are non-oliguric.
 - > Irreversible tubulointerstitial damage, however, is uncommon after discontinuing aminoglycoside.
 - We expect a diagnosis of acute renal failure beginning more than five days after the initiation of gentamicin;
 - ➤ Aminoglycoside nephrotoxicity correlates with → Frequency of aminoglycoside dosing
- Ototoxicity:
 - Streptomycin, tobramycin, and gentamycin are primarily vestibulotoxic
 - Kanamycin, amikacin, neomycin, and dihydrostreptomycin are preferentially cochleotoxic.
 - Cochlear toxicity that results in hearing loss usually begins in the <u>high frequencies</u> and is secondary to irreversible <u>destruction of outer hair cells in the organ of Corti</u>, predominantly at the <u>basal turn of the cochlea</u>
 - What is the explanation of progression of hearing loss or onset of hearing loss after cessation of aminoglycoside treatment?
 - Aminoglycosides are cleared more slowly from inner ear fluids than from serum
 - monitor the patient for cochleotoxic and vestibulotoxic effects <u>up to 6</u>
 <u>months after cessation of aminoglycoside</u> treatment is important.
 - What is the initial manifestation of early hearing loss?
 - increase in the threshold of highest frequencies (>4000 Hz).
 - what is the main teratogenic effect of aminoglycosides.
 - CN VIII toxicity

- · Transient myaesthenic syndrome
 - Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis;
 - large doses given during surgery have been responsible for a transient myaesthenic syndrome in patients with normal neuromuscular function.
- . What is the mechanism of resistance of Aminoglycosides?
 - Bacterial transferase enzymes;
 - they inactivate the drug by acetylation, phosphorylation or adenylation
- Why is the gentamycin <u>trough level</u> likely to be too high in patients with chronic renal failure?
 - Prolongation of the half-life
 - The usual half-life of gentamicin is between 2 and 3 h, although this can be considerably prolonged in patients with renal failure.

Administration

- There are two commonly used regimens for dosing gentamicin. Both require the patient's
 body weight to ensure accurate dosing. For patients who are over their ideal body weight,
 this value rather than the patient's actual weight should be used. Ideal body weight can be
 calculated using age, sex and height on a number of online applications.
 - The most commonly used dosing regimen in the UK is the <u>once daily regime</u>, which is thought to be associated with reduced toxicity whilst being effective against gram-negative infections.
 - It is not recommended for patients with a creatinine clearance of less than 60 ml/min.
 - The dose used is 7 mg/kg IV every 24 hours.
 - Levels should be monitored for patients on this regimen for 3 days or more, with a level taken 6-14 hours following the third dose. A nomogram is then used to determine whether the interval between doses should be altered.
 - 2. Patients with creatinine clearance of less than 60 ml/min are usually given a reduced dose of gentamicin with a multiple-daily dosing regimen. This may also be recommended by microbiologists for the treatment of serious gram-negative infections such as Pseudomonas. Dosing is dependent on creatinine clearance:
 - > >60 ml/min: 1.5-1.7 mg/kg IV every 8 hours
 - 40-60 ml/min: 1.2-1.5 mg/kg IV every 12 hours
 - > 20-40 ml/min: 1.2-1.5 mg/kg IV every 12-24 hours
 - <20 ml/min: 2 mg/kg loading dose then discuss with microbiology and pharmacy</p>
- On this regimen monitoring is typically initiated after the 3rd or 4th dose, which allows a steady-state to be reached. Peak levels should be taken 30 minutes following the end of the infusion, and a trough level taken before the next dose. The desired trough level is less than 2 micrograms/ml, with a peak level of 5-8 micrograms/ml.

Administering gentamic in conjunction with loop diuretics $\rightarrow \uparrow \uparrow$ risk of exacerbating renal and ototoxicity

Aminoglycosides Ototoxicity:

- > mechanism:
 - cochlear dysfunction (e.g., tinnitus, hearing impairment) by damaging cochlear cells, and/or
 - vestibulopathy (e.g., nausea, vomiting, dizziness, vertigo, oscillopsia, ataxia) by damaging hair cells of the inner ear.
 - nystagmus may be present as an early sign.
 - The vestibular dysfunction of gentamicin toxicity is typically bilateral; accordingly, there is no imbalance between right-sided and leftsided input to the central nervous system, so patients do not typically experience vertigo.
 - However, patients can experience <u>oscillopsia</u> and an abnormal <u>head</u> thrust test in both horizontal directions.
 - Oscillopsia is a visual disturbance in which stationary objects appear to oscillate.
 - occur only when the head is moving.
 - Quick movements of the head are associated with transient visual blurring.
 - This can cause difficulties with seeing signs while driving or recognizing people's faces while walking.
 - ⇒ Head thrust test (Head impulse test)
 - a physical examination maneuver to test for vestibular neuritis.
 - While the patient fixates on a target, the examiner administers brisk, horizontal head rotations to the side.
 - Considered positive if the patient is unable to maintain visual fixation, in which case the patient requires corrective saccades (quick eye movements) to re-fixate back to the target).

Macrolides

- Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.
- They are used against intracellular pathogens, including Mycoplasma and Legionella, and can also be used as alternatives in case of penicillin allergy.

Action

- Macrolides act by inhibiting bacterial protein synthesis by blocking translocation.
- Macrolides are bacteriostatic agents that inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome. If used in high doses, they may be bactericidal.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.
 - > bacteriostatic at low doses and bactericidal at high doses

Macrolides (erythromycin, azithromycin and clarithromycin), **aminoglycosides** and **chloramphenicol** \rightarrow **bind to bacterial ribosomes and disrupt protein synthesis**

Clarithromycin is a macrolide antibiotic with good gram positive cover and that of atypical

organisms. It's mechanism of action is via reversible inhibition of 50s ribosome subunit.

Mechanism of resistance

post-transcriptional methylation of the 23S bacterial ribosomal RNA

Adverse effects

- gastrointestinal side-effects are common. Nausea is less common with clarithromycin than erythromycin
- cholestatic jaundice: risk may be reduced if erythromycin stearate is used
- P450 inhibitor (see below)

Common interactions

- statins should be stopped whilst taking a course of macrolides. Macrolides inhibit the
 cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides
 concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis.
- Clarithromycin enhances anticoagulant effect of coumarins This is because warfarin is
 metabolised by the same CYP3A isozyme as clarithromycin. Clarithromycin, known to
 inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with
 elevations in drug concentrations that could increase or prolong both therapeutic and
 adverse effects of the concomitant drug.
- Clarithromycin is a potent inhibitor of CYP3A4, and as such may interfere significantly with metabolism of a number of medications, including theophylline, simvastatin, and cyclosporine as the most important drug interactions.
- The effect of warfarin and digoxin may also be potentiated by clarithromycin.

Erythromycin

- Was the 1st macrolide used clinically. Newer examples include clarithromycin and azithromycin.
- Erythromycin may potentially interact with amiodarone, warfarin and simvastatin
- Erythromycin would inhibit the metabolism of theophylline.
- Macrolides act by inhibiting bacterial protein synthesis.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

Erythromycin is used in gastroparesis as it has prokinetic properties, Promotes gastric emptying

Used in diabetic gastropathy,

Adverse effects of erythromycin

- GI side-effects are common
- Cholestatic jaundice: risk may be ↓ if erythromycin stearate is used
- P450 inhibitor
- associated with prolonged QT interval and torsades de pointes,

Quinolones

Ciprofloxacin - tendinopathy

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature. **Examples include:**

- ciprofloxacin
- levofloxacin

Mechanism of action

· inhibit topoisomerase II (DNA gyrase) and topoisomerase IV

Mechanism of resistance

mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration

Adverse effects

- lower seizure threshold in patients with epilepsy
- tendon damage (including rupture) the risk is increased in patients also taking steroids
 - > Rupture has been reported in the achilles, shoulder and hand.
 - > This may occur due to disruption of the extracellular matrix and depletion of collagen which is observed in animal models.
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children

Interaction & contraindication

- It should not be used with <u>drugs that prolong the QT interval</u> (eg erythromycin, tricyclic antidepressants) since there is an increased risk of cardiac arrhythmias
- · Contraindicated in left heart failure with reduced ejection fraction
- It should not be given at the same time as bivalent or trivalent cations (eg aluminium, iron) as these
 reduce absorption. Antacids → reduce quinolones absorption leading to therapeutic failure.
- Quinolone absorption is markedly reduced with antacids containing aluminium, magnesium and/or
 calcium and therapeutic failure may result. Other metallic ion-containing drugs, such as sucralfate,
 iron salts, and zinc salts, can also reduce absorption.
- The affinity of quinolones for the gamma-aminobutyric acid (GABA) receptor may induce CNS adverse effects; these effects are enhanced by some nonsteroidal anti-inflammatory drugs (NSAIDs).

Co-amoxiclav

- Because of cholestatic jaundice, prescription of co-amoxiclav is not recommended for longer than 14 days.
- If patient developed cholestatic jaundice → the co-amoxiclav should be withdrawn, and the combination avoided in future.

Probenecid

- Drugs can be excreted into the proximal convoluted tubule of the nephron by cation or anion transporters:
 - > cation transporters: basic drugs, eg quinine, pethidine, morphine
 - anion transporters: acidic drugs, eg penicillins, bendroflumethiazide, furosemide, cephalosporins
- The anion transporters are inhibited by probenecid, which can lead to increased plasma concentrations of acidic drugs
- probenecid used clinically to increase the plasma half-life and therefore the therapeutic duration of the drug
- For example, in the management of gonorrhoea infection, probenecid may be combined with oral
 penicillin to increase the half-life of the penicillin

<u>Sulfonamides</u>

Antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis.

Other uses

 The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and

- indapamide, among others), loop diuretics (including furosemide, bumetanide and torsemide) sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e. g. celecoxib) and acetazolamide.
- Sulfasalazine, in addition to its use as an antibiotic, is also utilized in the treatment of inflammatory bowel disease.
- **Co-trimoxazole:** sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of bacterial infections. The name co-trimoxazole is the British Approved Name, and has been marketed worldwide under many trade names including Septra, Bactrim, and various generic preparations. Sources differ as to whether co-trimoxazole usually is bactericidal or bacteriostatic

Vancomycin

Spectrum of the drug – MEC

- M MRSA
- E Enterococcus
- C Cl. difficle

Action

- · glycopeptide antibiotic
- Bactericidal
 - inhibits formation of peptidoglycan in bacterial cell walls, but a step earlier in the process compared to β-lactams

Side effects - RON

R - Red man syndrome

O – Ototoxicity

N - Nephrotoxicity

binds D-ala-D-ala moities of the peptides

Resistance

• D-ala-D-ala mutates to D-ala-D-lac, conferring resistance

Indications

- IV administration for serious, multidrug resistant Gram-positive infections
 - including methicillin-resistant Staphylococcus aureus infections (MRSA)
 - > including Enterococcus
 - including multidrug resistant Staph epidermidis
- Given orally for C. difficile → not systemically absorbed when given orally
 - > when antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening;
- prophylaxis,
 - > for endocarditis following certain procedures in patients at high risk for endocarditis;
 - for major surgical procedures involving the implantation of prosthetic materials or devices, e.g., cardiac and vascular procedures and total hip placement.

Side effects

- Red man syndrome
 - ➤ non-immunological reaction, <u>related to the rate of infusion</u> (infuse drug too fast → release of histamine → red rash)
 - If a patient experiences an infusion related reaction to vancomycin:
 - 1.Cease infusion
 - 2. Administer antihistamine (cetirizine10mg PO)
 - 3. If newly hypotensive consider adrenaline

 4. recommencement of vancomycin at a slower rate of infusion (doubling the time to infuse the solution, or changing to a continuous infusion).

Ototoxicity

- more likely in patients with high plasma concentrations, renal impairment or pre-existing hearing loss.
- may progress after drug withdrawal,
- > may be irreversible.
- Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.
- Nephrotoxicity
- Thrombophlebitis

Dosage

- loading dose: 25mg / kg (actual body weight)
- Maintenance dose: 15 mg/kg per dose (actual body weight)
 - > (15mg/kg 12-hourly if GFR ≥40mL/min, (maximum 2 grams per dose)
- When to start maintenance dose:
 - According to GFR level:
 - if GFR ≥ 40mL/min : 12 hours after loading dose
 - if GFR = 20-39 mL/min : 24 hours after loading dose
 - If GFR < 20mL/min: check trough level 24 hours after loading dose; wait for trough result prior to re-dosing.

Maintenance dose determination

GFR (m	L/min) [#]	GFR >90	GFR 60-90	GFR 40-59	GFR 20-39	GFR <20
Maintenance (dose	1.5g 12-hourly	1g 12-hourly	750mg 12-hourly	1g 24-hourly	1g every 2 to 7 days
Dosage Adjustment (intermittent	Trough level < 10mg/L	Convert to 1g 6-hourly	Convert to 1.5g 12-hourly	Convert to	Convert to 750mg	Monitor 48 hourly*
infusions)	Trough level 10 – 14.9 mg/L	Convert to 1.25g 8-hourly	Convert to 1.25g 12-hourly	1g 12-hourly	12-hourly [†]	Re-dose when trough <20mg/L
	Trough level 15 – 20mg/L	IN TARGET RANGE - no change required. Repeat trough levels twice weekly if vancomycin levels and renal function are stable. If not, more frequent monitoring is suggested*				
	Trough level 21 – 25mg/L	Convert to 1.25g 12-hourly	Convert to 750mg	Convert to 500mg	Convert to 750mg	Monitor 48- hourly*
	Trough level 26 – 30mg/L	Convert to 1g 12-hourly	12- hourly	12-hourly	24-hourly	Re-dose when trough <20mg/L
	Trough level > 30mg/L	Hold dose for Re-check lev renal function	el and recommer	nce at reduced do	se when level < 2	0mg/L. Review

Monitoring

- Vancomycin → requires plasma level monitoring (after three or four doses if the renal function is normal, or earlier if renal impairment is present)
- the best determinant of vancomycin efficacy is the AUC/MIC
- A 24-hour AUC/MIC of 400 or more is the target for clinical success
- AUC/MIC means: ratio of Area Under the Curve (plasma concentration vs time) to Minimum

- Inhibitory Concentration (Units are mg.hr/Litre)
- For practical reasons, a trough (pre-dose) plasma concentration is used as a surrogate measure of efficacy.
- Trough level means: a serum vancomycin level taken at the end of the dosing interval, approximately one hour prior to next dose
- The important level to measure here is the <u>trough level</u> as opposed to the <u>peak level</u> with gentamicin.
- the target vancomycin trough level for the treatment of (MRSA) bacteremia is 15 to 20 μg/ml to achieve an AUC/MIC of 400
- The trough level toxic threshold (30 mg/l).
 - > If trough level > 30 mg/l → Omit dose and restart when level <15 mg/l
 - dose omission is required to reduce the risk of significant complications (including ototoxicity and nephrotoxicity).
 - The BNF recommends trough levels of 15-20 mg/l for endocarditis.

Intravenous administration

- Doses of 1g should be administered over at least 60 minutes. For higher doses the duration of
 infusion should be extended by 30 minutes for each additional 500mg. This is recommended to
 reduce the risk of red man syndrome.
- The usual dilution is 5mg/mL; for fluid-restricted patients, concentrations of up to 10mg/mL may be used

Vancomycin Infusion Rate		
Dose	Minimum Infusion Duration*	
≤1 g	60 min	
1.1 - 1.5 g	90 min	
1.6 - 2.0 g	120 min	
> 2 g	Infuse at approx. 1 g per hour	

Which molecular change is responsible for vancomycin resistance?

- → D-ala D-ala to D-ala D-lac
 - Vancomycin resistance is involves its Binding sites the D-Ala-D-Ala.
 - terminal D-Ala is replaced by D-Lactate(D-Lac).

Linezolid

• is a type of oxazolidinones antibiotic class

Action

- inhibits bacterial protein synthesis by binding at the 50S subunit of the bacterial ribosome
 - linezolid occupies the A site of the 50S ribosomal subunit, inducing a conformational change that prevents tRNA from entering the site and ultimately forcing tRNA to separate from the ribosome
 - work on the first step of protein synthesis, *initiation*, unlike most other protein synthesis inhibitors, which inhibit *elongation*
- bacteriostatic

Spectrum, highly active against Gram positive organisms including:

- MRSA (Methicillin-resistant Staphylococcus aureus)
- VRE (Vancomycin-resistant enterococcus)
- GISA (Glycopeptide Intermediate Staphylococcus aureus)

Advantages

- high bioavailability (close to 100%) when given by mouth:
 - > the entire dose reaches the bloodstream, as if it had been given intravenously.

Adverse effects

- Bone marrow suppression (especially thrombocytopenia)
 - (reversible on stopping)
- · Peripheral neuropathy
- Gl upset
- Serotonin syndrome

Contraindications

- Concurrent use with monoamine oxidase inhibitors (MAOI) and selective serotonin reuptake inhibitors (SSRIs)
- · tyramine diet

Carbapenems

- Carbapenems are antibiotics used for multidrug-resistant (MDR) bacteria.
- members
 - imipenem (+ cilastatin)
 - normal kidneys break down imipenem with a dihydropeptidase
 - cilastatin, a selective dihydropeptidase inhibitor, is always given with imipenem
 - inhibits renal dihydropeptidase I, thereby decreasing inactivation of drug in renal tubules
 - cilastatin not needed for meropenem
 - meropenem
- Their use is primarily in people who are hospitalized.
- Like the penicillins and cephalosporins, they are members of the **beta lactam** class of antibiotics, which kill bacteria by binding to penicillin-binding proteins and **inhibiting cell wall synthesis**.
- Side effect
 - Gastrointestinal distress, skin rash and <u>seizures</u> are three common complications of carbapenem administration when there are high plasma levels.
 - > 5-10% of patients with penicillin allergy are also allergic to carbapenems

Meropenem

- Which Carbapanem antibiotic has less CNS toxicity? → Meropenem
- Meropenem is a carbapanem antibiotic that does not need to be coadministered with Cilastatin.

Trimethoprim

- Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.
- . It is combined with sulfamethoxazole for synergistic reasons

Mechanism of action

interferes with DNA synthesis by inhibiting dihydrofolate reductase

Adverse effects

- myelosuppression
- **transient rise in creatinine**: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug
 - ⇒ Trimethoprim interferes with tubular handling of creatinine and thereby leads to an increase in serum creatinine, without impairment of GFR.
- Megaloblastic anaemia may occur owing to folate deficiency

Quinupristin & dalfopristin antibiotics

Overview

- injectable streptogrammin antibiotic Only administered via a central line.
- combination of group A and group B streptogrammin respectively.
- · inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome

Spectrum

- most Gram-positive bacteria
- Particularly useful against multi- resistant Strep. pneumoniae and Staph. aureus.
- exception: Enterococcus faecalis*

Adverse effects

- thrombophlebitis (give via a central line)
- arthralgia
- P450 inhibitor

Tuberculosis: drug side-effects and mechanism of action

Drug	Most common side effects
Rifampicin	Orange bodily fluids, rash, hepatotoxicity, drug interactions
Isoniazid	Peripheral neuropathy, psychosis, hepatotoxicity
Pyrazinamide	Arthralgia, gout, hepatotoxicity, nausea
Ethambutol	Optic neuritis, rash

Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis,
- · orange secretions

Patients on rifampicin should be warned that their urine, tears and other secretions will develop a bright orange-red colour

- flu-like symptoms
- acute interstitial nephritis (pt may present with acute renal failure after 1 month of starting rifampicin)

Interaction

- Interact with oral contraceptive induces → failure of the oral contraceptive treatment
- Rifampicin is a potent hepatic enzyme inducer that increases the metabolism of many drugs, including all the steroid hormones
- Barrier contraceptives must be used during treatment with rifampicin and for 4-8 weeks after a course of rifampicin is completed

^{*}not to be confused with Enterococcus faecium, which is sensitive to Quinupristin & dalfopristin

Isoniazid

Isoniazid inhibits the P450 system

Isoniazid causes peripheral neuropathy

- · mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy:
 - Occurs in less than 1%
 - ➤ Those with N-acetyltransferase type-2 gene defect → resulting in abnormal isoniazid metabolism → predisposed to neuropathy
 - Prevented with 10 mg pyridoxine (Vitamin B6)
- hepatitis, raised transaminases in 10-20%
 - ➤ **Isoniazid-induced hepatitis** occurs in ~1% of individuals and is much commoner in people more than 35-years-old (risk of hepatitis is less than 0.3% in patients under 20 years; 2-3% risk in individuals over 50 years).
- agranulocytosis
- liver enzyme inhibitor
- isoniazid inhibits the conversion of tryptophan to niacin → nicotinic acid (niacin) deficiency
 → Pellagra (the 3 D's dermatitis, diarrhoea and dementia)
- systemic lupus erythematosus (SLE)-like syndrome.
- Isoniazid toxicity
 - > Isoniazid toxicity should be suspected in any patient with intractable seizures and profound metabolic acidosis with an elevated anion gap.
 - Intravenous pyridoxine (vitamin B6) is the treatment of choice.
 - > The acidosis may need to be corrected with bicarbonate.

Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- · hyperuricaemia causing gout
- arthralgia, myalgia
- hepatitis

Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- · optic neuritis: check visual acuity before and during treatment
- dose needs adjusting in patients with renal impairment

The main adverse effects of ethambutol are:

- loss of visual acuity
- restriction of visual fields
- colour blindness
- retrobulbar neuritis
- arthralgia.

Uncommonly it may be associated with

hyperuricaemia, and with interstitial nephritis. This is thought to occur less frequently than with rifampicin.

Antiviral agents

Antiviral agents				
Drug	Mechanism of action	Indication s	Adverse effects/toxicit y	
Aciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	HSV, VZV	Crystalline nephropathy	
Ganciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase	CMV	Myelosuppressio n/agranulocytosis	
Ribavirin	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA	Chronic hepatitis C, RSV	Haemolytic anaemia	
Amantadin e	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech	
Oseltamivir	Inhibits neuraminidase	Influenza		
Foscarnet	Pyrophosphate analog which inhibits viiral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnasaem ia, seizures	
Interferon-α	Human glycoproteins which inhibit synthesis of mRNA	Chronic hepatitis B & C, hairy cell leukaemia	Flu-like symptoms, anorexia, myelosuppressio n	
Cidofovir	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir)	CMV retinitis in HIV	Nephrotoxicity	

Which step is required for acyclovir activation?

→ Conversion to monophosphate form by viral thymidine kinase

HIV: anti-retrovirals

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Anti-retroviral agent used in HIV	About
Nucleoside Analogue	Examples: zalcitabine, zidovudine (AZT), didanosine,
Reverse Transcriptase Inhibitors (NRTI)	lamivudine, stavudine,
Protease inhibitors (PI)	Inhibits a protease needed to make virus able to survive outside the cell
	 Examples: indinavir, nelfinavir, ritonavir, saquinavir
Non-Nucleoside Reverse	examples: nevirapine, efavirenz
Transcriptase Inhibitors (NNRTI)	

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine
- general NRTI side-effects: peripheral neuropathy
- · zidovudine: anaemia, myopathy, black nails
- · didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

Protease inhibitors (PI)

- Protease inhibitors are multi-pathway inhibitors of rivaroxaban clearance and elimination.
- examples: indinavir, nelfinavir, ritonavir, saguinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

HIV: anti-retrovirals - P450 interaction

- nevirapine (NNRTI): induces P450
- protease inhibitors: inhibits P450

Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease, but appear much commoner in patients taking protease inhibitors.

Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors, but extremely high serum triglycerides have been documented in some patients treated with these drugs.

Oseltamivir (Tamiflu)

- Oseltamivir (Tamiflu) like its predecessor zanamivir (Relenza) functions as an antiviral through inhibition of the enzyme neuraminidase, thus slowing viral replication down rather than directly killing the virus particle.
- This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.
- Unlike inhaled zanamivir, oseltamivir is administered orally.
- Oseltamivir → It is of value in prophylaxis against influenza
- However, viral replication is rapid and to be effective the drug must be given as early as possible
 after the development of symptoms of flu and preferably within 48 hours.

Anti-fungal

- Nystatin is poorly absorbed through mucous membranes and is thus useful in oral, vaginal and enteric candidiasis
- Terbinafine is used to treat superficial mycoses such as dermatophyte infections
- Fluconazole is useful in candidiasis and central nervous system infections with Cryptococcus neoformans and is usually commenced after initial treatment with amphotericin and flucytosine
- **Itraconazole** is the agent of choice for non-life threatening blastomycosis and histoplasmosis it is also moderately effective against invasive aspergillosis
- Amphotericin B → treatment of Aspergilloma
 - ➤ The drug may exert either fungicidal or fungistatic activity, depending on its concentration at the site of infection and sensitivity of the organism
 - increases the permeability of the fungal cell wall by binding to ergosterol and forming micropores
 - ➤ side effect→ nephrotoxicity associated with hypokalaemia and hypomagnesaemia
 - > To decrease toxicity, newer lipid-bound preparations are now available

Griseofulvin

- Is not active against Candida albicans. It is active against trichophytons (tinea) and other dermatophytes.
- It is metabolised in the liver (note also it's an enzyme inducer). Only 0.1-0.2% excreted in urine.
- Treatment with griseofulvin is often needed for a long period, sometimes years, depending on the rate of nail growth.
- It is associated with drug-induced Stevens-Johnson syndrome

Diethylcarbamazine

Indication:

- Treatment of individual patients with certain filarial diseases.
- These diseases include: lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori; (ELEPHANTiasis) tropical pulmonary eosinophilia, and loiasis.

Overdose of antimalarial medications Chloroquine

Symptoms

- Nausea
- Headaches
- Visual disturbances
- Cardiac arrhythmias
- Convulsions
- Coma

Treatment

- Activated charcoal should be given to patients who present within 1 h
- The initial hypokalemia that occurs appears to be cardio-protective and should not be corrected for at least 8 h after the ingestion
- In patients with severe toxicity, high-dose (2 mg/kg) diazepam and adrenaline (0.25 pg/kg per min) have been shown to reduce mortality

Quinine toxicity (cinchonism)

Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed, dry skin and abdominal pain.

- Indications of Quinine:
 - antimalarial
 - prophylactic agent against leg cramps,
- The effect of Quinine toxicity, (known as cinchonism), may be fatal:
 - > In the short term:
 - cardiac arrhythmia (common) (ventricular tachyarrhythmias or fibrillation)
 - due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively
 - flash pulmonary oedema
 - Hypoglycaemia (common)
 - quinine stimulates pancreatic insulin secretion
 - Visual complications, including blindness, can occur and may be permanent
 - > in the long term
 - renal failure
- Differential diagnosis (Quinin vs Aspirin)
 - Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen
 - Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.
 - In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods.

Management

- Supportive
 - fluids, inotropes and bicarbonate as needed
 - positive pressure ventilation for pulmonary oedema.

> Avoid

- Lidocaine (lignocaine) should not be used in the management of cardiac arrhythmias as this can increase the risk of seizures
- Urine acidification is not recommended as whilst it increases quinine elimination, it also increases the risk of cardiotoxicity

Immunosuppressants

Ciclosporin (Cyclosporine)

Ciclosporin + tacrolimus - MOA: inhibit calcineurin thus decreasing IL-2

Ciclosporin side-effects: everything is increased - fluid, BP, K⁺, hair, gums, glucose

Mode of action

It acts by binding to <u>cyclophilin</u> forming a complex which → <u>inhibits calcineurin</u>, (a phosphotase that activates various transcription factors in T cells) → <u>reducing IL-2</u> release → decreases clonal proliferation of T cells → immunosuppression

Indications

- following organ transplantation
- · rheumatoid arthritis
- psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- ulcerative colitis
- pure red cell aplasia
- atopic dermatitis (AD) (T lymphocytes are involved in the pathophysiology of AD and increased production of cytokines particularly IL-4)

Adverse effects (note how everything is increased - fluid, BP, K*, hair, gums, glucose)

- Nephrotoxicity
 - Chronic interstitial nephritis is a major side-effect of ciclosporin
 - Fluconazole inhibits the metabolism of ciclosporin which increases the risk of ciclosporin nephrotoxicity.
- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection

Tremor

- > cause coarse tremor.
- In the first instance the dose should be reduced.
 - Usually the neurological side effects of cyclosporin are dose dependent.
- · increased risk for Squamous cell carcinoma
 - Cutaneous squamous cell carcinoma (SCC) is the second most common human cancer
 - transplant-associated SCC (TSCC), which occurs in immune-suppressed solid organ transplant recipients (OTRs) may be considerably more aggressive than SCC in immune competent patients, with metastatic rates as high as 8%
 - > IL-22 receptor is most highly expressed in TSCC and is induced by cyclosporine A.
 - Treatment with anti–IL-22 antibody decreases SCC tumor number and tumor burden.

Note:

Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

Cyclosporine A immunosuppression drives catastrophic <u>squamous cell</u> <u>carcinoma</u> through IL-22 (September 2016)

Monitoring

- These patients are seen monthly to have their blood pressure, urea, and electrolytes checked.
- indications for stopping cyclosporine treatment:
 - > Difficult to control hypertension
 - > increase in creatinine by more than 30% from baseline

Tacrolimus

Mode of action

• similar to the action of ciclosporin

Tacrolimus vs Ciclosporin:

- It has a very similar action to ciclosporin (inhibits calcineurin, reducing IL-2 release)
- The action of tacrolimus differs from ciclosporin in that it <u>binds to a protein called FKBP</u> rather than cyclophilin
- Tacrolimus is <u>more potent</u> than ciclosporin and hence the incidence of organ rejection is less.
- However, nephrotoxicity and impaired glucose tolerance is more common

Indications

- · immunosuppressant to prevent transplant rejection.
- · Other T-cell medicated diseases
 - Eczema (as ointment)
 - > Sever refractory uveitis after bone marrow transplant
 - Vitiligo

Monitorina

• Tacrolimus levels can be affected by concomitant use of other drugs and changes in gut absorption, and so **need to be monitored carefully**.

Many side effects of tacrolimus are similar to cyclosporine A, but <u>tacrolimus does not</u> <u>cause gingival hyperplasia or hirsutism</u>

Sirolimus

Overview

- A macrolide compound
- Also known as rapamycin

Mode of action

- binding with intracellular FKBP-12 protein → inhibition of mTORC1→ ↓ cytokine-induced
 T-cell proliferation → immunosuppression
- Sirolimus binds to the immunophilin FK binding protein 12 (FKBP12), and the drugimmunophilin complex acts on the Target of Rapamycin (rapamycin being the original name of sirolimus) to interrupt stimulation of cell proliferation via the interleukin-2 receptor.
- What is the target of action of sirolimus?
 - ⇒ FK binding protein 12 (FKBP12)

Indications

· treatment of acute rejection.

Adverse Effects

- Pancytopenia
- Hyperlipidemia
- Peripheral edema
- · Insulin resistance
 - ➤ Inhibition of mTORC2 → diabetes- like symptoms

Azathioprine

Azathioprine → check thiopurine methyltransferase deficiency (TPMT) before treatment

- Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis → Impaired DNA synthesis
- A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.
 - ⇒ The enzyme activity of thiopurine methyltransferase (TPMT) is under the control of a genetic polymorphism.
 - ⇒ 90 % of the population have normal or high (TPMT) enzyme activity. 10 % have intermediate levels
 - ⇒ One in 300 people have no functional enzyme activity.
 - ⇒ Several groups of patients have developed azathioprine induced myelosuppression linked to TPMT deficiency.

Adverse effects include

- bone marrow depression → Pancytopenia
 - ⇒ It suppresses lymphocyte numbers and function
- nausea/vomiting
- · pancreatitis
- Hepatotoxicity
- 100-fold increased risk of skin cancers and lymphomas.

Monitoring

 (BNF) suggest monitoring CBC, LFTs and U&E every 3 months once patients are established and stable on azathioprine treatment.

interaction

- Azathioprine and 6-MP are metabolized by xanthine oxidase. Therefore, allopurinol—a xanthine oxidase inhibitor—increases the risk of azathioprine and 6-MP toxicity.
- A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.
 - ⇒ Allopurinol acts by inhibition of xanthine oxidase and thus inhibits the metabolism of 6-mercaptopurine, an active metabolite of azathioprine.
 - ⇒ The prodrug azathioprine is metabolised to its active compound 6-mercaptopurine (6-MP). 6-MP undergoes catabolic oxidation to 6-thiouric acid by xanthine oxidase.
 - ⇒ Allopurinol has a peak onset of action of one to two weeks and works by inhibiting xanthine oxidase.
 - ⇒ Co-administration of (Azathioprine + Allopurinol) → accumulation of 6-MP (6-MP toxicity) → ↑ risk of myelosuppression (aplastic anaemia)
 - ⇒ if concomitant use is to occur, a dose reduction in azathioprine by 25% is advised with regular blood count monitoring.

Usage in pregnancy

Azathioprine can be used in pregnancy without significant risk to the fetus

Methotrexate

Action

- Methotrexate is an <u>antimetabolite</u> which <u>inhibits dihydrofolate reductase</u>, an enzyme essential for the synthesis of purines and pyrimidines
 - Methotrexate inhibits dihydrofolate reductase, thereby inhibiting the production of tetrhydrofolate required for thymidine and purine synthesis.
 - inhibits purine and pyrimidine synthesis by competing for the active site of dihydrofolate reductase (by competitive inhibition).
 - ⇒ It is cytotoxic during the S-phase of the cell cycle, and has a greater toxic effect on rapidly dividing cells.
 - ⇒ Take 6 -12 weeks to achieve full affect

Indications

- · rheumatoid arthritis
- psoriasis (Methotrexate would be the only correct treatment for someone with erythrodermic psoriasis)
- · acute lymphoblastic leukaemia

Adverse effects

- mucositis
- myelosuppression
- Macrocytosis is seen as a consequence of long term methotrexate therapy.
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis
 - ⇒ What is the toxicity of Methotrexate (MTX) at the liver?
 - Macrovesicular fatty change

Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

Prescribing methotrexate

methotrexate is taken weekly, rather than daily

- FBC, U&E and LFTs need to be regularly monitored.
 - ⇒ The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- Folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg once weekly, can be increased by 2.5 mg every 6 weeks, to a maximum of 20 mg weekly (Ref: oxford handbook of practical drug therapy)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- do not prescribe with aspirin or NSAIDs → ↓ methotrexate excretion → ↑ toxicity
- avoid prescribing anti-folate antibiotics trimethoprim or cotrimoxazole concurrently increases risk of marrow aplasia
- In the circumstances of infection one should consider temporarily stopping methotrexate as it is an immunosuppressant.

Interaction

- OAT-1 inhibitors
 - Methotrexate is a substrate for the OAT-1 renal transporter and levels of methotrexate are therefore affected by decreased renal function.
 - OAT-1 inhibitors include drugs such as <u>probenecid</u>, and therefore should not be used in conjunction with methotrexate.
- Omeprazole
 - Omeprazole is also known to affect clearance of methotrexate; this interaction is not thought to be via OAT-1, but is <u>thought to be related to inhibition of breast</u> cancer resistance protein, which is responsible for methotrexate transport.

Monitoring

- Clinicians are recommended to check FBC fortnightly until 6 weeks after the last dose increase.
 - Provided it is stable, it can be checked monthly thereafter until the dose and disease is stable for one year.
 - > Thereafter, monitoring is guided by clinical judgement. If white cell count is less than 3.5, neutrophils less than 2 or platelets less than 150, methotrexate should be withheld pending discussion with the specialist team.
 - An MCV greater than 105 fL warrants checking B12, folate and TSH and treating any abnormality. If these are normal, discuss with the specialist team.
- Liver function tests should be checked three monthly. If there is an unexplained decrease in albumin, or AST/ALT twice the upper limit of normal, the specialist team should be informed.
- Urea, creatinine and electrolytes should be checked six monthly. If the estimated
 glomerular filtration rate falls below 50 mL/minute, methotrexate should be withheld until the
 result has been discussed with the specialist team.

Drug	MOA	
Mycophenolate mofetil	inhibits inosine monophosphate dehydrogenase	
Azathioprine	metabolised to the active compound mercaptopurine a purine analogue that inhibits DNA synthesis. purine synthesis inhibitor	
Methotrexate	antimetabolite which inhibits dihydrofolate reductase	

Methotrexate overdose

Methotrexate overdose → Folinic acid

- Methotrexate is a folic acid antagonist which can result in multi-organ failure in overdose.
- medication errors with respect to rheumatoid arthritis are not uncommon.
 - Patients occasionally find it difficult to understand that they must take their medication weekly as opposed to daily.
- Calcium folinate is a potent antagonist for the effects of methotrexate on the haematopoeic system, given by IV infusion at doses up to 75mg in the first 12hrs. This can then be followed by doses of 6-12mg every 4hrs.
- Folinic acid is the antidote and should be given intravenously as soon as possible, regardless of the liver function tests.
- Blood transfusion may also be required in exceptional circumstances.
- Where massive overdose of methotrexate has occurred, hydration and urinary alkalinisation may be an option.
- Standard dialysis is ineffective in removing methotrexate, although intermittent high flux dialysis may be of value.

Mycophenolate mofetil

Mode of action

- inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis as T and B cells are particularly dependent on this pathway it can reduce proliferation of immune cells
- A growing number of studies have demonstrated the efficacy of mycophenolate in SLE, especially in the context of lupus nephritis.
- Mycophenolate is an anti-purine drug that selectively depletes B and T lymphocytes (preferentially targeting activated cells). The result of this mode of action is that neutropenia is rare, which would be advantageous in (SLE) patients complicated by an autoimmune neutropenia.
 - the most appropriate agent for (SLE) which complicated by an autoimmune neutropenia
- adverse effects
 - Pancytopenia
 - Hypertension
 - Hyperglycemia

Hydroxychloroquine

- Hydroxychloroguine ocular toxicity includes:
 - Keratopathy
 - > Ciliary body involvement
 - Lens opacities (Lenticular deposits)
 - > Retinopathy.
 - Retinopathy is the major concern; the others are more common but benign.
 - The incidence of true hydroxychloroguine retinopathy is exceedingly low.
 - Risk factors include:
 - Daily dosage of hydroxychloroquine
 - Cumulative dosage
 - Duration of treatment
 - Coexisting renal or liver disease

- Patient age, and
- Concomitant retinal disease.
- Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia.
- They can also be asymptomatic.
- Most patients with advanced retinopathy have a bull's eye (also known as target, as in darts) fundoscopic appearance. All patients have field defects including paracentral, peri-central, and central and peripheral field loss.
- Regular screening may be necessary to detect reversible premaculopathy.
- Cessation of the drug is the only effective management of the toxicity.

Sulfasalazine

Side effects

- hypersensitivity,
- · myelosuppression,
- · macrocytosis, and
- · azoospermia in males.

sulfasalazine toxicity

- · There are numerous signs of sulfasalazine toxicity.
- Rash and oral ulceration should be asked about and, if severe, the drug should be withheld until specialist advice has been sought.
- Nausea, dizziness and headache can be common and sometimes necessitate dose reduction.
- If patients present with abnormal bruising or sore throat an urgent CBC should be done, and sulfasalazine withheld until results are available.

Monitoring

- CBC
 - > CBC should be monitored monthly for the first 3 months.
 - Sulphasalazine should be withheld until discussion with the specialist team if:
 - The white cell count is less than 3.5
 - Neutrophils is less than 2, or
 - Platelets are less than 150.
 - If (MCV) > 105 fl, vitamin B12, folate and TSH should be checked and treated if found to be abnormal. If these are all normal it should be discussed with the specialist team.
 - ➤ If counts remain normal within the first 3 months, CBC can be checked 3 monthly.
- Liver function tests (LFTs)
 - should also be checked monthly for the first 3 months.
 - If either AST or ALT are more than twice the upper limit of normal, sulfasalazine should be withheld until discussion with the specialist team.
 - If the LFTs remain normal for the first 3 months, monitoring can be decreased to 3 monthly.

If, following the first year, the dose has not been increased and blood results have been stable, the frequency of monitoring can be reduced to every six months for the second year of treatment. Thereafter monitoring is not required, although CBC and LFTs should be checked one month after any dose increase.

Leflunomide

- an immunosuppressive disease-modifying antirheumatic drug (DMARD), used in active moderate-to-severe rheumatoid arthritis and psoriatic arthritis.
- It is a pyrimidine synthesis inhibitor.
- achieves its effects by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which plays a key role in the *de novo* synthesis of uridine monophosphate (rUMP), which is required for the synthesis of DNA and RNA. Hence, leflunomide inhibits the reproduction of rapidly dividing cells, especially lymphocytes.

Side effects

- Hepatotoxicity (occurring in 15-20% of cases)
 - > most hepatic events occur within the first 6 months of use.
- signs of leflunomide toxicity should be monitored. If the patient develops a rash or itch
 dose reduction should be considered, with or without the addition of antihistamines. If
 severe, leflunomide should be stopped and washout considered.
- Hair loss, headaches and gastrointestinal upset may also warrant dose reduction or washout.
- A blood pressure of greater than 140/90 mmHg should be treated as per NICE guidelines. If it remains elevated, stop leflunomide and consider washout.
- Weight should be monitored, and a weight loss of greater than 10% should be identified. If no other cause can be found, consider dose reduction or washout.
- If there is increasing shortness of breath, **pneumonitis** should be considered and leflunomide should be stopped.
- Leflunomide reduces sperm count.

Monitoring

- LFT
 - > (LFTs) should be checked monthly for 6 months and, if stable, 2 monthly thereafter.
 - ➤ If AST or ALT is between 2 and 3 times the upper limit of normal, and the leflunomide dose is more than 10 mg daily, the dose should be reduced to 10 mg and LFTs rechecked weekly until normalised. If the ALT and AST are returning to normal, the patient should be left on 10 mg per day. It the LFTs remain elevated, leflunomide should be stopped and discussed with the specialist team.
 - ➤ If the AST or ALT is more than 3 times the upper limit of normal, the LFTs should be rechecked within 72 hours. If they remain more than 3 times the reference range, leflunomide should be stopped and washout considered (cholestyramine and activated charcoal).
 - It is important to note that the half-life of leflunomide is usually 2 weeks (mean 14) therefore if a rapid response is required, washout should be considered.

• CBC

- (CBC) should be checked monthly for six months and, if stable, two monthly thereafter.
- ➤ White cell count less than 3.5, neutrophils less than 2 or platelets less than 150 should be discussed with the specialist team, and leflunomide withheld until this has taken place.

Poisoning & Toxicology

Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Treatment	
Paracetamol	Management	
Salicylate	Management urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning haemodialysis	
Opioid/opiates	Naloxone	
Benzodiazepines	Flumazenil	
Tricyclic antidepressants	IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias dialysis is ineffective in removing tricyclics	
Lithium	Management mild-moderate toxicity may respond to volume resuscitation with normal saline	

Toxin	Treatment	
	 haemodialysis may be needed in severe toxicity sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion 	
Warfarin	Vitamin K, prothrombin complex	
Heparin	Protamine sulphate	
Beta-blockers	Management	
Ethylene glycol	Management has changed in recent times ethanol has been used for many years works by competing with ethylene glycol for the enzyme alcohol dehydrogenase this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning fomepizole, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol haemodialysis also has a role in refractory cases	
Methanol poisoning	Management	
Organophosphate insecticides	Management	
Digoxin	Digoxin-specific antibody fragments	
Iron	Desferrioxamine, a chelating agent	
Lead	Dimercaprol, calcium edetate	
Carbon monoxide	Management 100% oxygen hyperbaric oxygen	
Cyanide	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate	
Sarin (organophosphorus)	Pralidoxime → reactivates acetyl cholinesterase enzyme. It should be used in the first few hours.	

Drug poisoning: Hypersalivation

Hypersalivation is seen with:

- Parasympathomimetic agents
- Insecticides
- Arsenic
- Strychnine
- · Chlormethiazole, and
- · Clozapine.

Other poisoning signs

Acneiform rash around the buccal cavity → Solvent abuse

Nasal septum perforation (and hypertension) → Cocaine abuse

Drug poisoning: Altered serum glucose in unknown overdose

Alteration in serum glucose concentration, in addition to other clinical signs and symptoms, can be helpful in diagnosing the ingestion of an unknown drug:

Drugs induce hyperglycaemia	Drug induce hypoglycaemia
Corticosteroids,	 insulin, sulphonylureas,
 thiazide diuretics, 	Salicylates
 theophylline, 	 sodium valproate,
 iron (during the initial period 	propranolol,
after overdose),	 iron (later if hepatic failure ensues)
caffeine and	
B2-agonists	

Drugs cleared by alkalization of the urine

The clearance of which drug would be increased by alkalization of the urine?

- Weak acids are ionized in an alkaline environment, and this lessens their tubular absorption.
- Alkalization of urine, achieved by IV infusion of sodium bicarbonate, can thereby be used to increase the urinary elimination of:
 - 1. barbiturates,
 - 2. salicylates and
 - 3. isoniazid.

Measurement of drug concentrations

- Measurement of drug concentrations is clinically important for relatively few compounds.
- Drug concentrations are particularly important for those compounds where the concentration is
 predictive of serious toxicity in an otherwise asymptomatic patient.

Compounds where measurement of drug concentration is clinically indicated:

- Paracetamol
- Theophylline
 - Theophylline concentrations predict the risk of seizures and cardiac toxicity in both acute and chronic toxicity
 - ➤ Patients who have ingested more than 10 mg kg⁻¹ of theophylline should receive repeated doses of activated charcoal.
- Digoxin
- Iron

- Lithium
- Salicylate
- Ethylene glycol
 - ➤ An ethylene glycol concentration of >50 mg dl⁻¹ is a possible indication for haemodialysis and a definite indication for 4-methylpyrazole (4MP) or ethanol infusion
- Methanol
 - ➤ A methanol level of greater than 50 mg dl-1 is a possible indication for haemodialysis and a definite indication for 4MP or ethanol infusion.
 - haemodialysis usually considered at methanol concentrations <u>above 20 mmol/l</u> (approximately 90 mg/dl).
- Ethanol
- Anticonvulsants
 - Measurement of anticonvulsant concentrations will confirm ingestion but do not substantially influence treatment in overdose, which is supportive care.
- Paraquat
 - > non-selective contact herbicide
 - paraquat concentrations are useful for confirming ingestion and defining prognosis but do not influence treatment, which is predominantly supportive care

Drug toxicity in renal failure

- A wide range of drug-handling processes occur in the kidney:
 - ⇒ Filtration
 - ⇒ tubular secretion
 - ⇒ active and passive tubular reabsorption
- The overall renal clearance of drugs declines in parallel with falls in the glomerular filtration rate and creatinine clearance

Norpethidine

- In patients with renal impairment pethidine is metabolised to norpethidine, but at this stage
 metabolism stops and norpethidine accumulates rather than being excreted through the
 kidneys
- Norpethidine is toxic and is associated with a risk of seizures

Morphine

- A similar accumulation of morphine 6-glucuronide occurs after morphine administration in patients with renal impairment, which may lead to narcosis
- fluid overloaded + pin point pupils in a patient taking morphine with renal impairment
 → the most likely cause of his symptoms → Renal failure leading to accumulation of
 morphine (not overdose) (masterclass 2017 part 2)
 - ⇒ Patients with relapsed ovarian cancer may develop an obstructive nephropathy due to pelvic recurrence. If they are on morphine they may get accumulation of this drug and signs of opiate toxicity superimposed on the signs of renal failure.

Other drugs

- Other drugs where physiologically active metabolites accumulate leading to toxicity in renal failure include:
 - ⇒ nitroprusside (active metabolite thiocyanate)
 - ⇒ allopurinol (accumulation of oxypurinol leads to rash and allergy)

Characteristic smells of toxins/poisons

Certain toxins/poisons have characteristic smells that can assist in the identification of substances taken. Below is a list of well-recognised smells/odours and the poisons/toxins for which they are characteristic.

Garlic: Arsenic, seleniumBitter almonds: Cyanide

• Rotten eggs: Hydrogen sulphide, mercaptans

Wintergreen: Methyl salicylateMothballs: Naphthalene

Arsenic toxicity

The combination of mixed sensorimotor polyneuropathy in the presence of possible exposure to pesticides in a farmer would suggest a diagnosis of chronic arsenic poisoning.

- Arsenic is a heavy metal which is a natural component of the earth's crust.
- exists in organic or inorganic . It is highly toxic in its inorganic form.
 - ⇒ organic arsenics found in fish and seafood are non-toxic
- Arsenic exposure is usually occupational or environmental
- routes of exposure include:
 - ⇒ Groundwater most often becomes contaminated naturally
 - Arsenic contamination of groundwater is widespread
 - most common in Bangladesh, West Bengal and india
 - ⇒ **Occupational exposures:** toxic waste sites and traditional medicines.
- Features
 - ⇒ Acute
 - GI (nausea, vomiting, hemorragic gastroenteritis, garlic breath)
 - CNS (coma, seizures)
 - ⇒ Chronic
 - Skin changes: dermatitis, hyperkeratosis & hyperpigmentation
 - The first symptoms of long-term exposure
 - the most common effect of chronic exposure
 - Keratoses on the palms and soles are characteristic.
 - . occur after a minimum exposure of approximately five years
 - may be a precursor to skin cancer.
 - Mees lines: leukonychia striata (transverse white lines on the finger nails)
 - Abdominal pain
 - Sensory-motor Peripheral neuropathy
 - Diabetes
 - Cancers (lung, bladder, skin).
- Arsenic can interfere with the mechanism of hemoglobin synthesis and the ribosomes may form dot-like precipitates, called basophilic stippling, at the periphery of RBCs.
- Basophilic stippling is also found in:
 - ⇒ thrombotic thrombocytopenic purpura. in hemoglobin H disease (rarely)
 - ⇒ megaloblastic anemia.
 - It indicates a RBC cell line maturation defect in the bone marrow.
- The hematological effects of arsenic toxicity include:
 - ⇒ Anemia
 - ⇒ Pancytopenia

- ⇒ Hemolysis in some cases
- Management
 - ⇒ Acute exposure → Chelation:
 - Consider chelation therapy in patients who are symptomatic and/or have urine concentration >200 mcg/L.
 - DMPS is the chelation agent of choice.
 - DMSA is an alternative (oral preparation only, so unsuitable if the patient is vomiting).
 - ⇒ Chronic exposure
 - arsenic-free drinking water, to reduce the risk of further disease
 - It is recommended that all patients with skin lesions be given multivitamins.

Drugs altered pupil size

Many drugs can cause changes in pupil size as detailed below:

- Dilated pupils (mydriasis):
 - > sympathomimetic drugs, eg cocaine, dopamine, amphetamines
 - > anticholinergic drugs, eg antihistamines, atropine, tricyclic antidepressants
- Constricted pupils (miosis):
 - > sympatholytic drugs, eg opiates, phenothiazines, clonidine, sodium valproate
 - cholinergic drugs, eg organophosphates, pilocarpine

Charcoal

- reduce drug absorption from the gastrointestinal tract, and interrupting enterohepatic recirculation.
- Which factor would be most strongly influence your decision to administer or avoid oral activated charcoal?
 - Absence of bowel sounds
 - It is generally safe, but should be administered only in patients who are able to protect their airway. The absence of bowel sounds may indicate a paralytic ileus, which is surprisingly common after overdose, and which is associated with an increased risk of charcoal aspiration and pneumonitis.
- Iron, lithium and other cations are not adsorbed by charcoal; alcohols including ethanol, methanol and ethylene glycol are not adsorbed either.
- Activated charcoal is capable of adsorbing around 10% of its own weight, so administration of charcoal 50 g might be expected to adsorb around 5 g of drug.
- should normally be administered within 1 hour of drug overdose, but may be effective when administered after a longer interval, particularly after modified-release preparations.

Multi-dose activated charcoal

When Activated charcoal can be repeatedly given to increase elimination of the poison?

- ⇒ When the drug circulates through the enterohepatic circulation
- Multi-dose activated charcoal means giving 50 g of activated charcoal every 3-4 h
- It is useful in patients who have taken significant amounts of salicylates, and should be continued until plasma salicylate concentrations have peaked
- It is also useful in the management of patients who have taken drugs with significant enterohepatic circulation (carbamazepine, phenobarbital, theophylline and quinine) and sustained-/modified-release preparations
- It is contraindicated in patients with signs of bowel obstruction,

Methanol poisoning

Overview

- Methanol, like ethanol, is metabolised by alcohol dehydrogenase to form formaldehyde. Formaldehyde is then further metabolised by aldehyde dehydrogenase to formic acid.
- Formate formation leads to:
 - severe metabolic acidosis, and
 - crystals forming within the eye can lead to so called 'snow field' cataract formation.

Feature

- Early signs (are due to methanol) include:
 - ⇒ Nausea and vomiting
 - ⇒ Headache.
 - ⇒ Confusion.
- later signs (are due to its metabolite, formic acid)
 - ⇒ high gap metabolic acidosis
 - Anion gap = (Na + K) (Cl + HCO₃); normal range 7-17 mmol/L.
 - Although elevated, the lactate level does not account for the anion gap.
 - ⇒ visual problems, retinal injury, including blindness (methanol-associated visual loss)
 - accumulation of formic acid → a form of optic neuropathy

Differential diagnosis

 The differential diagnosis of this form of a <u>high anion gap metabolic acidosis</u> is (SLUMPED) (salicylates, lactic acidosis, uremia, methanol/ethylene glycol, paraldehyde, ethanol, and diabetic ketoacidosis).

Similarities between Methanol and ethylene glycol intoxication

- Both are causes a very similar biochemical and clinical picture.
- Both require the enzyme alcohol dehydrogenase for metabolism.
- Both are treated with fomepizole or ethanol, which inhibit alcohol dehydrogenase
- Both can present with metabolic acidosis, hyperpnea and tachypnea, coma, seizures, and hypotension.
- The fruity smell suggests ketosis.

Differences between Methanol and ethylene glycol intoxication

- From history
 - Methanol is pure distilled alcohol, more likely to be consumed by those with a history of alcohol abuse.
 - Ethylene glycol is antifreeze, usually consumed by those with suicidal intent or history of deliberate self-harm.
- From examination
 - ⇒ eye signs (macular oedema and poor pupillary responses) → methanol
 - In exams, cases involving methanol toxicity often involve patients not meeting your gaze or asking for the lights to be switched on, as well as the more traditional visual acuity results.
 - Methanol leads to the formation of <u>formate</u>, which causes retinal damage with optic disc hypemia and edema, blindness, and basal ganglia infarcts.
 - ⇒ Ethylene glycol causes the formation of calcium oxalate crystals, leading to renal.

failure and **hypocalcemia** (→ tetany)

- Oxalate crystals are a specific sign of ethylene glycol toxicity.
- formate is the toxic metabolite of methanol
- oxalic acid is the toxic metabolite of ethylene glycol

Management

- fomepizole or ethanol → Inhibition of methanol metabolism by alcohol dehydrogenase is
 the treatment of choice.
 - \Rightarrow 1st line \Rightarrow fomepizole which is an inhibitor of alcohol dehydrogenase.
 - \Rightarrow 2nd line \Rightarrow If fomepizole is not available, then ethanol is recommended.
- sodium bicarbonate if necessary to correct severe acidaemia (pH <7.20)
- Haemodialysis

Treatment is aimed at:

- 1. Eliminating formic acid (alkaline diuresis or haemodialysis).
- 2. Correcting acidosis with IV bicarbonate.
- 3. Preventing metabolism of methanol to formic acid by administering IV ethanol.

Ethylene glycol toxicity

Ethylene glycol toxicity management - fomepizole. Also ethanol / haemodialysis

• Ethylene glycol is a type of alcohol used as a coolant or antifreeze

Features of toxicity are divided into 3 stages:

- Stage 1: symptoms similar to alcohol intoxication: confusion, slurred speech, dizziness
- Stage 2: metabolic acidosis with high anion gap and high osmolar gap. Also tachycardia, hypertension
- Stage 3: acute renal failure
 - ⇒ renal, respiratory and cardiac failure.
 - ⇒ Multi-organ failure is thought to occur at least in part <u>due to widespread deposition</u> of calcium oxalate crystals around 12 h after the initial insult.

Management

- treatment is often given based on clinical suspicion due to a delay in obtaining ethylene glycol levels in most centres.
- fomepizole, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol
 - ⇒ prevents metabolism of ethylene glycol to <u>oxalic acid</u>, responsible for the <u>acidosis</u> and renal failure
 - ⇒ Because of the potential formation of calcium oxalate, <u>calcium levels should also</u> be assessed.
- ethanol has been used for many years
 - ⇒ works by competing with ethylene glycol for the enzyme alcohol dehydrogenase
 - ⇒ this limits the formation of toxic metabolites (e.g. <u>glycoaldehyde and glycolic acid</u>) which are responsible for the **haemodynamic/metabolic features** of poisoning
- IV fluids with bicarbonate to correct the metabolic acidosis in severe lactic acidosis.
- · Calcium gluconate for hypocalcemia,

• haemodialysis also has a role in refractory cases

Fomepizole - used in ethylene glycol and methanol poisoning - competitive inhibitor of alcohol dehydrogenase

Isopropyl alcohol (Isopropanol) intoxication

Acidosis + eye signs → methanol poisoning
Acidosis without eye signs → ethylene glycol poisoning
Ketosis without acidosis → isopropyl alcohol poisoning

Overview

- It is a clear colorless liquid with a BITTER TASTE and **fruity odor**.
- commonly used as a rubbing alcohol and as a solvent in hair-care products, skin lotions and home aerosols.
- Also found in products including cleaners, disinfectants, antifreezes, cosmetics, solvents, inks, and pharmaceuticals.
- Inexpensive and can be a substitute for ethanol.
- the second most common alcohol intoxication next to ethanol.
- It is twice as potent as ethanol as a central nervous system depressant but without an early elation phase.

Feature:

- Severe isopropanol poisoning results in CNS and respiratory depression and circulatory collapse.
- GIT and CNS symptoms are predominating,
- <u>alcohol</u>, benzodiazepines, <u>isopropyl alcohol</u>, lithium, and organophosphates may all lead to <u>miosis</u> (constriction of the pupil)
- Large ingestions can result in coma.
- The most common metabolic effects are an increased osmol (osmolal) gap, ketonemia, and ketonuria
- metabolic acidosis unlike in other alcohols intoxication is not present, this is because isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone, (a ketone is not an acid).
 - ⇒ therefore, ketone appear in breath and in urine.
- Isopropyl alcohol intoxication can be remembered as "ketosis without acidosis".
- Another unique finding is "pseudo renal failure" or ISOLATED false elevation of creatinine with a normal BUN.

Diagnosis:

- An osmol gap, ketonemia, and/or ketonuria <u>without metabolic acidosis</u>, along with a fruity or sweet odor on the breath and CNS depression support the diagnosis.
- Although ethylene glycol, methanol, and ethanol ingestions result in anion gap <u>and</u> osmolar gap, <u>isopropyl alcohol results in only</u> an osmolar gap.
 - ⇒ Osmolar gap = Osmolality Osmolarity
 - Osmolality is <u>measured</u> in laboratory by osmometers
 - Osmolarity is calculated = (2 x [Na+]) + [glucose] + [urea]
 - normal = < 10

- the units of osmolality are mOsm/kg of solute
- the units of osmolarity are mOsm/L

Treatment:

- supportive care (is the mainstay of management)→ Patients usually make a full recovery
- hemodialysis → elimination of isopropanol and acetone → only in severe life-threatening poisonings.

Ecstasy poisoning

- Ecstasy is an amphetamine derivative (MDMA, 3,4-Methylene-Dioxy-Meth-Amphetamine) use became popular in the 1990's during the emergence of dance music culture
- is a semi-synthetic hallucinogen used as a recreational drug.

Clinical features

- · neurological: agitation, anxiety, confusion, ataxia
- · cardiovascular: tachycardia, hypertension
- hyponatraemia
- Hyperventilation
- hyperthermia
- rhabdomyolysis

Management → supportive (no specific antidote)

- Cold intravenous fluids if the core temperature is over 39 °C
- dantrolene may be used for hyperthermia if simple measures fail
- and/or paralysis and ventilation
- · Treatment of associated hyperthermia

Opioid misuse

Acute confusion and visual hallucinations are common symptoms of opioid toxicity and pin point pupils and myoclonas are common signs.

Opioids are substances which bind to opioid receptors. This includes both naturally
occurring opiates such as morphine and synthetic opioids such as buprenorphine and
methadone.

Features of opioid misuse

- rhinorrhoea
- · needle track marks
- pinpoint pupils
- drowsiness
- watering eyes
- yawning
- symptoms of neurotoxicity (for example, hallucinations, myoclonus and delirium)
- · respiratory depression

Complications of opioid misuse

- viral infection secondary to sharing needles: HIV, hepatitis B & C
- bacterial infection secondary to injection: infective endocarditis, septic arthritis, septicaemia, necrotising fasciitis
- · venous thromboembolism
- · overdose may lead to respiratory depression and death
- · psychological problems: craving
- · social problems: crime, prostitution, homelessness

Emergency management of opioid overdose

- IV or IM **naloxone**: has a rapid onset and relatively short duration of action
- intravenous naloxone (0.4 mg), repeated up to a total dose of 2 mg depending on clinical response.
- The half-life of naloxone is shorter than that of opioids, hence if the patient wakes up it can be anticipated that he will 're-narcose'. A naloxone infusion may be necessary.

Harm reduction interventions may include

- needle exchange
- offering testing for HIV, hepatitis B & C

Management of opioid dependence

- · patients may be offered maintenance therapy or detoxification
- NICE recommend <u>methadone</u> or <u>buprenorphine</u> as the first-line treatment in opioid detoxification
- compliance is monitored using urinalysis
- detoxification should normally last up to 4 weeks in an inpatient/residential setting and up to 12 weeks in the community
- Naltrexone can be used to help prevent relapse in the treatment of Opioids dependency
 - ⇒ Naltrexone is a long-acting opioid antagonist.
 - ⇒ It can be used as an adjunct to psychosocial treatments to prevent relapse <u>in</u> detoxified patients who were formerly dependent on opioids.
 - ⇒ Naltrexone should only be initiated in specialist clinics.
 - ⇒ Patients should have remained opioid-free for at least 7–10 days before naltrexone is started.
 - ⇒ Naltrexone has also been shown to be useful for relapse prevention in those who misuse alcohol.

Dihvdrocodeine

- Dihydrocodeine is an opiate analgesic and when taken in overdose has a number of toxic effects.
- It acts as a respiratory depressant leading to reduced respiratory rate.
- It can cause bradycardia and hypotension in large doses.
- Pupillary constriction is a diagnostic feature in opiate overdose.
- It is also a central nervous system depressant and therefore causes coma in overdose.

Pain relief

 Titrating the dose of morphine needed for analgesia should be done with rapidly acting formulations of morphine, and once adequate analgesia is obtained sustained-release morphine can then be substituted (at the same total daily dose)

Analgesia in opiate users (eq: on methadone)

- Discontinuation of methadone may result in symptoms of acute opiate withdrawal and this is not recommended
- Continuation of methadone and consideration of analgesics with a different mode of action (ie non-steroidals such as parenteral diclofenac) is recommended

Opioid withdrawal

- The symptoms and signs of opioid withdrawal include dysphoric mood, yawning, insomnia, nausea, vomiting, diarrhoea, muscle aches, lacrimation / rhinorrhoea, pupillary dilatation, piloerection, sweating and fever.
- Initially give 10 mg of methadone syrup and wait about 60 min to determine its effect.
 Continue administering in 10 mg doses until symptoms are under control. It is rare to exceed a total dose of 40 mg over 24 hours.

Morphine

Side-effects including:

- Nausea, vomiting
 - ⇒ Nausea affects up to two-thirds of patients starting morphine but in the majority of these it is self-limiting to within 1 week.
 - ➡ Haloperidol is the first-line drug for opioid-induced nausea, kidney disease and hypercalcaemia
- constipation
- drowsiness, confusion
- others, including: bronchospasm, angioedema, urinary retention, ureteric or biliary spasm, dry mouth, sweating, rash, facial flushing, vertigo, tachycardia, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, mood change, hallucinations, seizures (adults and children) and miosis, headache and allergic reactions (including anaphylaxis) and decreased libido or potency
- pruritus in some patients, secondary to intradermal histamine release.
 - changing to an alternative opioid such as oxycodone, which is less likely to cause itching, may be more appropriate
- raised intracranial pressure
- Muscle rigidity may occur with high doses
- biliary sphincter constriction → Elevated liver enzymes
- Large doses can lead to respiratory depression, circulatory failure and coma

Morphine vs pethidine

- Morphine acts for four to five hours while pethidine works for two to three hours.
 - ⇒ This means that pethidine would have to be given at more frequent intervals to produce the same analgesic effects as morphine.

Pethidine

- Meperidine (Pethidine) is a full opioid agonist at <u>mu</u> receptors.
 - ⇒ the only opioid that acts as an antimuscarinic
- Pethidine is contraindicated in most cases of sickle cell pain. It is metabolized into a cerebral irritant that can lead to clonus, seizures, or altered mental status.
- Pethidine is preferred to morphine in the preoperative management of biliary colic and in the management of acute diverticulitis.
 - Pethidine is comparable to morphine in its sedative and tranquillizing effects, <u>but the analgesia and respiratory depression it produces are of shorter duration</u>, and it induces less smooth muscle spasm.
- It is largely metabolized in the liver and the end-products are excreted in the urine.
- Contraindications
 - Bronchial asthma, emphysema or heart failure secondary to chronic lung disease.
 - Increased intracranial pressure, head injury or brain tumour.
 - > Severe hepatic impairment, adrenocortical insufficiency, hypothyroidism.
 - Convulsive disorders, acute alcoholism, delirium tremens.
 - > Use of monoamine oxidase inhibitors within the previous 14 days.

Buprenorphine

Action

- partial opiate agonist at mu and kappa opioid receptors.
 - meaning that by occupying the receptor, it <u>doesn't achieve the effects of full agonism</u>, and thus has <u>less addictive potential versus other opiates</u>.
 - Due to the fact that buprenorphine is a partial agonist, at higher doses it displays "functional antagonism", meaning that by occupying the receptor it blunts the effects of other full opiate agonists.
- It also has a long half-life of up to 32hrs.
 - > This means that it can be utilised in cases of addiction to short-acting opiates such as diamorphine because it reduces the highs, and thus addictive potential, associated with these agents.

Interaction

- Since buprenorphine is a <u>partial</u> agonist at opioid receptors, it will antagonise the action of a <u>full</u> agonist such as morphine
- therefore it is appropriate to substitute morphine for buprenorphine, but not to add the two together

MRCPUK- part-1- jan- 2017: What is the mode of action of buprenorphine?

→ Partial mu opioid receptor agonist

Cocaine

- · Cocaine is an alkaloid derived from the coca plant.
- cocaine toxicity becoming a much more frequent clinical problem.

Mechanism of action

· cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

Cardiovascular effects

- myocardial infarction
 - ⇔ cocaine-induced MI is thought to be related to coronary artery spasm
 - It is probably caused by stimulation of the α-adrenergic receptors in smooth muscle cells. In addition, cocaine increases endothelin-1 (a vasoconstrictor) and decreases nitric oxide (vasodilator).
- both tachycardia and bradycardia may occur
- hypertension
 - ⇒ (Blockage of noradrenaline (norepinephrine) re-uptake leads to →tachycardia, & ↑↑BP)
 - QRS widening and QT prolongation
- aortic dissection

Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia
- haemorrhagic stroke
- cocaine-induced spinal cord infarct:
 - ⇒ The constellation of quadriparesis, spinothalamic sensory loss with sparing of posterior columns and sphincter dysfunction is most suggestive of an anterior spinal cord syndrome.
 - The areflexia may reflect spinal cord shock.

- With a C3/4 spinal cord lesion, it is not surprising that the patient has respiratory difficulties.
- detection of cocaine in the urine suggesting he was using it

Psychiatric effects

- agitation (inhibition of dopamine re-uptake → psychomotor agitation)
- psychosis
- hallucinations (serotonin re-uptake blockade leads to → hallucinations)

Others

- hyperthermia which may lead to rhabdomyolysis and renal failure
- metabolic acidosis
- rhabdomyolysis

Management of cocaine toxicity

- · in general benzodiazipines are generally first-line for most cocaine related problems
 - Agitation, seizures and hypertension are best treated with benzodiazepines (such as midazolam) initially.
 - ⇒ Diazepam is useful for the treatment of anxiety and may precipitate a small reduction in blood pressure, **but will not treat coronary artery vasospasm.**
 - Calcium channel blockers (such as nifedipine) can be used as a second line treatment for hypertension if benzodiazepines are ineffective.
- chest pain:
 - ⇒ benzodiazipines + glyceryl trinitrate.
 - Other option include calcium antagonists,
 - ⇒ If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension:
 - ⇒ benzodiazipines + sodium nitroprusside
- Beta blockers should be avoided in cocaine associated myocardial ischaemia or infarction as they
 can potentiate coronary vasoconstriction.
 - Beta blockers are contraindicated as they can cause unopposed alpha activity and worsen hypertension.
- Intubation and ventilation will lower blood pressure and improve the ischaemia
 - the most appropriate next intervention if diazepam fail to control the acute symptoms (eg: seizure)
 - Whilst IV sodium valproate and IV phenytoin may be effective in terminating the recurrent seizures, these options would cost precious time with respect to controlling blood pressure and pyrexia

MRCPUK-Part-1-January 2016 exam: A 23-year-old man found 'collapsed' in the bathroom at a house party. Then C/O severe abdominal pain + blood in his stool. What is the single most likely cause of his abdominal pain? Ischaemic colitis (Ischaemic colitis is a recognised phenomenon following cocaine ingestion and should be considered if patients develop abdominal pain or rectal bleeding)

Heroin withdrawal

- The following are all signs of heroin withdrawal:
 - rhinorrhoea
 - diarrhoea
 - nausea and vomiting
 - lacrimation
 - irritability and restlessness, which are cardinal features

Heroin substitutes in medical management of withdrawal

- Both <u>buprenorphine</u> and <u>methadone</u> may be considered for use as heroin replacements
- Buprenorphine may be associated with less risk in overdose, but NICE recommends that unless circumstances dictate otherwise, methadone should be the first-choice therapy
- Co-abuse of alcohol and benzodiazepines may drive preferential use of buprenorphine, as these
 agents increase the risk of significant CNS depression

Benzodiazepine overdose

Benzodiazepine overdose is best managed supportively and with airway protection and ventilation if needed. Flumazenil should be avoided unless for reversal of anaesthesia

Overview

- toxicity with sedative drugs is the second most common agent after analgesic agents- in some parts of the United Kingdom.
- Benzodiazepine overdose is very rarely life-threatening unless associated with the coingestion of alcohol or other respiratory depressants

Features

- CNS depression: lethargy, somnolence, hyporeflexia
- Ataxia
- Slurred speech
- Mild hypotension
- · Respiratory depression

Treatment

- Supportive therapy
 - > GCS ≤ 8: endotracheal intubation
 - > Hypotension: fluid resuscitation
- Antidote: flumazenil
 - > Routine use of flumazenil for benzodiazepine overdose is not recommended
 - A general rule of thumb is that a benzodiazepine toxicity syndrome should never be reversed with the antidote drug flumazenil unless it was you who gave the benzodiazepine.
 - Most cases of benzodiazepine overdose occur in patients who are on chronic benzodiazepine therapy for psychiatric illness, anxiety or seizures.
 - Rapid reversal of benzodiazepines with flumazenil can precipitate withdrawal symptoms and seizures in patients with benzodiazepine dependence.
 - If a seizure is precipitated by flumazenil the treatment is to give further benzodiazepines.
 - Indications
 - Severe respiratory depression
 - Overdose in benzodiazepine-naive patients (e.g., accidental ingestion in children, periprocedural oversedation with benzodiazepines)
 - reversal of anaesthesia.

Cathinone toxicity

- NRG-1 is a synthetic cathinone drug which is increasingly used recreationally.
- Pharmacologically it is a derivative of phenylpropanone which is a naturally occurring psychotrope in khat (Catha edulis).
- Synthetic cathinones became increasingly popular in the last ten years as an alternative to ecstasy
 since they were cheaper, easier to produce and initially were unrestricted. As legislation changes,
 chemical substitutions are made to molecular moieties to create similar drugs to avoid restrictions.
- All exert their effect by increasing synaptic concentrations of noradrenaline, dopamine and serotonin, giving users the sensation of euphoria, detachment and wellbeing as well as upregulation of the sympathetic system.

• Toxicity is often seen due to lack of regulation of constituents and active ingredients

Features

- Tachycardia and hypertension may be seen due to the sympathomimetic effects of the drug and in some cases myocardial ischaemia can be seen.
- In the majority of cases of toxicity, however, similar to ecstasy toxicity, hyponatraemia and serotonin syndrome are seen. Hyponatraemia occurs as a consequence of significant water intake to reduce body temperature. Serum sodium levels may be markedly low and patients may present seizing.
- **Serotonin syndrome** is due to massive flooding of synapses with liberated serotonin and causes agitation, confusion, muscle hyperactivity with fasciculations, hypertonia and clonus.
- Creatine kinase and white cell counts are often raised and body temperature may be extremely high.

Treatment

- If there is evidence of neurological compromise with an accompanying hyponatraemia, rapid correction of sodium is recommended with infusion of 3% saline solution at a maximum rate of 1ml/kg/hour.
- 0.9% saline solution is not recommended in patients with hyponatraemia and agitation due to the
 risk of worsening the hyponatraemia.

Cannabinoids

- Cannabinoids are derived from the resin of cannabis sativa.
- 9-tetrahydrocannabinol (9-THC) is its most important pharmacologically active constituent.
- Oral bioavailability of THC, whether given in the pure form or as THC in marijuana, is low and extremely variable, ranging between 5% and 20%, with effects occurring 0.5-3 hours later.
- Bioavailability of THC in a marijuana cigarette or pipe also rarely exceeds 10-20%.
- Naloxone and other opioid receptor antagonists block the analgesic actions of cannabinoids.
- Synthetic cannabinoids reduce arachidonic acid-induced inflammation by inhibiting eicosanoid production.

Cyanide poisoning

cyanide mechanism of action → Inhibition of enzyme cytochrome oxidase c

- Cyanide may be used in:
 - > insecticides.
 - photograph development and
 - production of certain metals.
- Acute cyanide toxicity may occur secondary to burning plastics in the house fire.
- Toxicity results from reversible inhibition of cellular oxidising enzymes
- Cyanide ions inhibit mitochondrial cytochrome oxidase, preventing aerobic respiration, which
 is an essential part of the mitochondrial electron transfer chain (ETC). It therefore interferes with the
 basic process of cellular respiration, preventing the formation of ATP and causing rapid cell death.

Presentation (classical features: brick-red skin, smell of bitter almonds)

- manifests in normal oxygen saturations, a high pO2 and flushing (or 'brick red' skin) brought on by the excess oxygenation of venous blood. (it is important to note that the blood gas sample given is venous rather than arterial)
- acute: hypoxia, hypotension, headache, confusion
 - increased anion gap, consistent with high lactate (generated by anaerobic respiration due to the inability to use available oxygen).

- > very high lactate and high venous pO2 fit better with cyanide toxicity.
- · chronic: ataxia, peripheral neuropathy, dermatitis

Management

- supportive measures: 100% oxygen
- definitive: hydroxocobalamin (intravenously), also combination of amyl nitrite (inhaled), sodium nitrite (intravenously), and sodium thiosulfate (intravenously)
- The recommended treatment for moderate cyanide toxicity in the UK is one of three options:
 - 1. Hydroxocobalamin,
 - has the best side-effect profile and speed of onset compared with other treatments
 - 2. dicobalt edetate.
 - only given when the patient is tending to lose or has lost consciousness.
 - When the patient is fully conscious, it is unlikely that the extent of poisoning warrants the use of Dicobalt Edetate Injection.
 - Dangerous if given without confirmed cyanide poisoning
 - Other antidotes such as hydroxocobalamin or sodium thiosulphate are preferred.
 - 3. sodium thiosulfate

Hydroxocobalamin

- also known as vitamin B12a and hydroxycobalamin,
- is an injectable form of vitamin B 12
- indications
 - vitamin B 12 deficiency
 - cyanide poisoning,
 - Leber's optic atrophy,
 - toxic amblyopia (Nutritional optic neuropathy)
 - a condition where a toxic reaction in the optic nerve results in visual loss.
 - Various poisonous substances may cause the condition as well as nutritional factors.
 - Tobacco amblyopia is a form of toxic amblyopia caused by tobacco containing cyanide.

Sarin gas

- Sarin gas and related agents cause inhibition of the enzyme acetylcholinesterase, causing levels of
 acetylcholine to build up in the nervous system causing prolonged sustained contraction of the
 diaphragm. This hinders and eventually paralyses normal breathing.
- · Sarin has muscarinic and nicotinic effects.
 - ⇒ Muscarinic effects:
 - Paralysis
 - Fasciculations
 - Hyperglycaemia, and
 - Ketosis.
 - - Hypotension
 - Meiosis
 - Dyspnoea, and
 - Gl disturbance.

Arsenic

- Arsenic causes inhibition of the enzyme pyruvate dehydrogenase which is necessary for the
 conversion of pyruvate to acetyl CoA. This also interferes with the basic process of cellular
 respiration, as pyruvate formed during glycolysis cannot be changed to acetyl CoA to enter the
 Kreb's cycle.
- Arsenic and mustards → cause mutational damage to DNA → ↑ risks of skin and haematological malignancy in the longer term.
- Arsenic can also accelerate atherosclerosis.

Acid poisoning

Pathology

· Acids cause injury by coagulative necrosis

Presentation

- · Acid effects are mainly topical, with corrosive burns to the mouth, oropharynx and stomach
- They are less likely than alkalis to cause significant localised damage to the oesophagus
- Aspiration can lead to inflammation and a chemical pneumonitis

Management

- Neutralisation of acids is not appropriate, since this can generate increased heat and so exacerbate any injury sustained
- Gastric lavage is contraindicated due to the increased risk of oesophageal perforation
- Management consists of supportive care and early endoscopy
- Early surgical intervention is required to prevent mediastinitis, from which there is a high mortality, in those patients with signs or symptoms of perforation
- Hydrofluoric acid causes significant hypocalcaemia as it binds calcium,
 - even small amounts (topically or ingested) can produce significant hypocalcaemia and be rapidly fatal
 - in cases of significant topical exposure, patients should be monitored for signs of systemic hypocalcaemia
 - patient treated with intravenous calcium supplementation if required .
 - > Calcium gluconate applied both topically and injected around the burn may be required
 - Systemic fluorosis may occur as a complication

Alkali poisoning

- Alkalis cause saponification (liquefactive necrosis) of tissue
- Neutralisation of alkalis is not appropriate, as this can generate increased heat and so exacerbate
 any injury sustained
- · Assuming survival, fluorosis may lead to further problems later on

Radiosensitiser drugs

Radiosensitiser drugs → radiation toxicity

radioconomicor drugo y radiation toxiony		
 dactinomycin, 	 hydroxyurea 	
 metronidazole 	 paclitaxel 	
 5-fluorouracil 	mitomycin C	
 gemcitabine 	 topotecan 	
 cisplatin 		

Radioprotector

Amifostine is a radioprotector

Management of body packers

- The management of body packers and body stuffers is relatively straightforward
- Abdominal radiographs may show some packages in the gastrointestinal tract they appear as air halos trapped within the packages, but not all packages may contain trapped air
- In patients with no signs of drug-associated toxicity, whole-bowel irrigation with polyethylene glycol will clear the gastrointestinal tract of all the swallowed packages
- Endoscopy may also be useful in removing packages that are still in the stomach, but packages should be carefully removed to prevent damage and drug release
- Gastric lavage may increase the risk of package rupture
- Laxatives may also help the packages to pass naturally, but paraffin-based laxatives should not be
 used since they increase the risk of package rupture
- Surgical intervention to remove all the remaining packages may be necessary in patients who start to develop signs of drug toxicity, since the strength and amount of drug in each package is unknown

Heavy metal poisoning

Causes

- · lead: most common
- mercury
- manganese
- cadmium
- thallium

Lead poisoning

- Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of **abdominal pain and neurological signs**
- Lead can also be absorbed through the skin and by inhalation.

Aetiology: ingestion of:

- lead-containing compounds, deliberate (pica) or inadvertent
 - > Patients with learning disabilities may be prone to lead poisoning due to pica.
- · contaminated water from old lead water pipes
- occupation, such as a painter have a lead exposure while stripping the walls in old houses.
- certain traditional remedies such as ayurvedic medicines

Features

- abdominal pain
- nausea
- constipation
- peripheral neuropathy (mainly motor) due to demyelination
- fatique
- blue lines on gum margin (only 20% of adult patients, very rare in children)
- · may be associated with anterior uveitis or iritis

Laboratory tests

- Whole blood lead levels:
 - > <10 µg/dL normal.
 - > 10 μg/dL may cause impaired cognitive development in children.
 - > >45 μg/dL GI symptoms in adults and children.
 - > >70 μg/dL high risk of acute CNS symptoms.

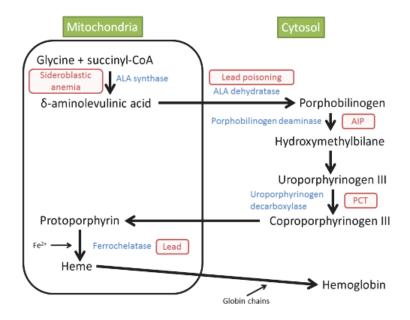
> >100 µg/dL - may be life-threatening.

Investigations

- Abdominal radiographs are essential to see if there is any unabsorbed lead present, which can be removed by whole-bowel irrigation
- The blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- · full blood count:
 - > microcytic anaemia.
 - > Blood film shows red cell abnormalities including:
 - basophilic stippling
 - This occurs due to accumulation of (RNA) in the RBCs due to inhibition of pyrimidine 5 nucleotidase by lead.
 - clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
 - > the most appropriate intervention
 - The recommended dose is 10 mg/kg three times per day for five days, followed by 10 mg/kg twice per day for two weeks.
- FDTA
 - This is used IV or IM, which makes administration less convenient than DMSA.
 - It is considered for patients with symptoms of severe acute lead poisoning.
- Dimercaprol
- Penicillamine
- succimer



Mercury poisoning

Features

- paraesthesia
- visual field defects
- ataxia
- dysarthria
- hearing loss
- irritability
- renal tubular acidosis
- Chronic poisoning from the inhalation of mercury vapour results in a classic triad of tremor, neuropsychiatric disturbance and gingivostomatitis

Cadmium (Cd) poisoning

Workers in zinc factories are at risk of cadmium (Cd) poisoning.

Feature

- Bone pain, osteopenia
- Renal failure.
 - The Cd-protein complex is mainly taken up by proximal tubular cells. This may give rise to a tubular proteinuria
 - may also cause a Fanconi syndrome-like presentation, with amino aciduria and phosphaturia.
 - Prolonged renal tubular toxicity may cause glomerular damage.
 - Another renal effect of prolonged Cd exposure is calcium phosphate stones.

Thallium poisoning

Features

- · painful polyneuropathy
- mood change
- alopecia

Treatment is chelation therapy with oral Prussian Blue.

Iron overdose

· Undissolved iron tablets are radio-opaque

Presentation

- Early features of iron overdose are due to the direct corrosive effects of iron and include vomiting, diarrhoea and gastrointestinal bleeding
- Typically, there is then a latent phase of up to 24 h when the patient is asymptomatic
- This is then followed by widespread organ failure
- Initial hyperglycaemia can occur following significant ingestion of iron, but hypoglycaemia can be seen later in cases of severe poisoning with associated hepatic failure
- In patients who recover, there may be <u>long-term GI strictures and possible gastrointestinal</u> obstruction due to the initial corrosive effects of iron

Treatment

- Iron is a metal and therefore will not be adsorbed by activated charcoal
- Patients with serum iron concentrations over 90 mmol/l, as well as those with signs of severe toxicity, require **chelation therapy with desferrioxamine**

LSD intoxication

Lysergic acid diethylamide (LSD)

- · No medicinal use.
- Recreationally used as a hallucinogen and for its ability to alter human perception and mood.

Pharmacodynamics:

- LSD is primarily a non-selective 5-HT agonist.
- LSD may exert its hallucinogenic effect by interacting with 5-HT2A receptors as a partial agonist and modulating the NMDA receptor-mediated sensory, perceptual, affective and cognitive processes.
- LSD mimics 5-HT at 5-HT1A receptors, producing a marked slowing of the firing rate of serotonergic neurons.

Features

- hallucinations
- heightened sense of awareness
- synaesthesia
- palinopsia

New recreational drugs

Drug types	Street names
Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL)	G, Geebs or Liquid Ecstasy
Synthetic agonists of the CB1 receptor	Spice
Methoxetamine (derivative of ketamine)	Mexxy
Benzylpiperazine	Exodus, Legal X, Legal E
Nitrous oxide	Hippie crack

Paracetamol overdose

Overview

- it is the most common agent of intentional self-harm
- · it is the most common cause of acute liver failure
- As little as 10–15 g (20–30 tablets) in an adult or 150 mg/kg of paracetamol taken within 24 h may cause severe hepatocellular necrosis and, less frequently, renal tubular necrosis.

Pathophysiology

- → Paracetamol is conjugated to glucuronic acid and sulphate under normal conditions.
- →In overdose these processes become saturated and the drug is then results in a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI)
- → (NAPQI) inactivated by glutathione, rapidly preventing any harm.
- → If the glutathione supply is depleted then a toxic metabolite is formed.

After ingestion of a therapeutic dose:

- The liver normally conjugates paracetamol with <u>glucuronic acid/sulphate</u>.
- and the resulting non-toxic metabolites are excreted in the urine.
- About 4% of a therapeutic dose is metabolised by the cytochromes P450, mainly CYP2E1,

- to a potentially toxic intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI).
- NAPQI combines with intracellular glutathione to become a non-toxic mercapturate derivative with urinary excretion.

after ingestion of an overdose:

- the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*.
- the normally minor CYP2E1 pathway becomes important.
- This produces a toxic metabolite (N-acetyl-B-benzoquinone imine)
 - ⇒ *this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin
- Normally <u>glutathione</u> acts as a defence mechanism by conjugating with the toxin forming the <u>non-toxic mercapturic acid</u>.
- If glutathione stores run-out, the toxin leads to cell death of hepatocytes and renal tubules

Paracetamol overdose: risk factors

The following groups of patients are at an increased **risk of developing hepatotoxicity** following a paracetamol overdose:

- patients taking liver enzyme-inducing drugs (rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort)
- malnourished patients (e.g. anorexia or bulimia, cystic fibrosis, hepatitis C, alcoholism, HIV
 ⇒ ↓ glutathione stores
- · patients who have not eaten for a few days
- Human immunodeficiency virus (HIV) positive patients.

Investigations

- Paracetamol level: take paracetamol level
 - 1. four hours post-ingestion, or
 - 2. as soon as the patient arrives if:
 - Time of overdose is greater than four hours.
 - Staggered overdose (in staggered overdoses, the level is not interpretable except to confirm ingestion).

Management

The essentials of management are:

- Check paracetamol level <u>four hours after ingestion</u>, check levels against the Rumack-Matthew nomogram.
- 2. Gastric lavage if large dose ingested (more than 7.5 g) and/or presenting within eight hours of ingestion; consider oral charcoal.
- 3. Give N-acetylcysteine or methionine.
- 4. Hourly BMs monitored.
- 5. Check INR 12 hourly.

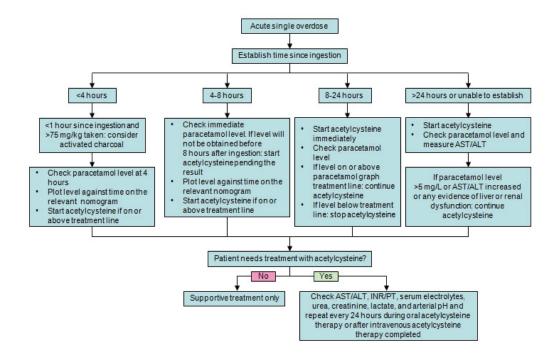
if patient present with ingestion of non-significant amount (<150mg/kg) and timing of ingestion is known (1- 4 hrs) → No immediate action

- A single dose of activated charcoal (50g for adults) can be given up to 1 hour after ingestion
- Acetylcysteine should be started immediately or empirically when:
 - ⇒ if a significant amount has been taken (>150mg/kg).

- ⇒ Serum paracetamol level: 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion
- ⇒ patients who present late (8-24 hours)
- ⇒ Serum paracetamol level is not available within an 8-hour time window
- ⇒ If there is any doubt about the timing of the ingestion (including a staggered overdose over one hour or more).
- ⇒ Patients are unconscious or have a suspected overdose.
- Hepatotoxicity is unlikely if it is >24 hours since last ingestion of paracetamol and all the following apply:
 - 1. Patient is asymptomatic.
 - 2. Paracetamol concentration is <5 mg/L.
 - 3. INR is 1.3 or less.
 - 4. ALT is less than 2 times upper limit of normal.
 - ⇒ If all of the above criteria are fulfilled then acetylcysteine may be stopped, and the
 patient discharged with the advice to return if he or she becomes symptomatic
 (vomiting, abdominal pain).

Repeated supratherapeutic ingestion

- ⇒ Patients who have ingested <75 mg/kg in a period of 24 hours are very unlikely to develop hepatotoxicity.
 </p>
- ⇒ Those who have ingested 75 mg, or less/kg/24 hours of paracetamol require no treatment.
- ⇒ Those who have ingested 75-150 mg/kg/24 hours should be considered for acetylcysteine (based on amount ingested, timing, and other relevant features)
- ⇒ Those who have ingested >150 mg/kg/24 hours are treated with acetylcysteine.



Prescribing N-acetyl cysteine (NAC)

- Action:
 - it is a precursor of glutathione and hence can increase hepatic glutathione production
- Root and administration:
 - Acetylcysteine is the treatment of choice and is given intravenously (in the US and some other places it is still occasionally given orally).
 - Although the oral route is simpler, it frequently causes nausea and vomiting and is unpleasant. Additionally, the standard oral regimen is 72 hours in duration compared with 21 hours intravenously.
 - Acetylcysteine should be administered by intravenous infusion preferably using Glucose 5% as the infusion fluid. Sodium Chloride 0.9% solution may be used if Glucose 5% is not suitable.
- Indications:
 - N-Acetylcysteine is recommended in all cases where the paracetamol overdose exceeds 150 mg/kg body weight
 - ➤ All patients with a plasma paracetamol level ≥ 100 mg/L at 4 hours or ≥ 15 mg/L at 15 hours after ingestion should receive acetylcysteine regardless of risk factors for hepatotoxicity.
 - The paracetamol level is not used to guide treatment in the setting of a staggered overdose, and N-acetylcysteine should be given without delay to reduce the risk of liver failure.
 - In the case of staggered overdose or unclear timing of overdose, acetylcysteine should be given.

· When to be started:

- ⇒ N-acetylcysteine is most effective when administered within 8 h of ingestion
- ⇒ If acetylcysteine is started within 8 hours of the ingestion, hepatotoxicity is extremely unlikely.
- ⇒ The urgency of treatment is underlined by the fact that the incidence of hepatotoxicity is worse if treatment is delayed.
 - Trials of N-acetylcysteine suggest that the incidence of hepatotoxicity is 1% in those treated within eight hours as opposed to 46% in those treated after 16 hours.

Infusion rate:

- ➤ The new guidelines have increased the recommended <u>duration of the first</u> <u>infusion to 60</u> minutes from 15 minutes previously.
- > The MHRA now recommends extending the time of the initial infusion from 15 minutes to 60 minutes in order to reduce the incidence of adverse reactions.

Doses:

- ⇒ The full course of treatment with acetylcysteine comprises of 3 consecutive intravenous infusions.
- The patient should receive a total dose of 300 mg/kg body weight over a 21-hour period.
 - First infusion
 - Add the appropriate volume of acetylcysteine injection to <u>200 mL of</u> infusion fluid and infuse over 1 hour.
 - 2. Second infusion
 - Add the appropriate volume of acetylcysteine injection to <u>500 mL of</u> infusion fluid and infuse over the next 4 hours.
 - 3. Third infusion
 - Add the appropriate volume of acetylcysteine injection to <u>1 litre</u> of infusion fluid and infuse over the next 16 hours.

Reactions to NAC

- Features:
 - (eg: patient became flushed and hypotensive)
- > Mechanism:
 - Reactions to NAC are well recognized and are not related to hypersensitivity.
 - The majority of dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine.
 - Any 'hypersensitivity-like' reactions are more likely to be anaphylactoid in nature (i.e. not immunologically mediated) and therefore may not occur on repeated exposure.

> Management:

- NAC can almost always be safely restarted, and total dose safely administered after symptomatic treatment.
- Even if a patient has a history of a previous reaction to intravenous acetylcysteine, the benefits outweigh the risks and patient should receive treatment.
- IV chlorpheniramine and restart NAC infusion once symptoms resolved
- What is the most appropriate next step after iv antihistamine?
 - ⇒ Re-start the N-acetylcysteine infusion at half rate
- Oral methionine may be an alternative but is definitely second line.
 - Patients often have an associated history of alcohol intake and episodes

of vomiting, which can affect the pharmacokinetics of oral medications.

Paracetamol overdose during pregnancy

- resulting toxic metabolites can cross the placenta and lead to hepatocellular necrosis of maternal and fetal liver cells.
- NAC can bind the toxic metabolites in the mother and fetal circulation as it crosses the
 placenta.
- NAC appears to be safe during pregnancy and therefore should be administered.

King's College Hospital criteria for liver transplantation in paracetamol-induced acute liver failure

List for transplantation if:

- Arterial pH <7.3 or arterial lactate >3.0 mmol/L after adequate fluid resuscitation; OR
- If all three of the following occur in a 24-hour period:
 - ⇒ Creatinine >300 µmol/L.
 - \Rightarrow PT >100 seconds (INR >6.5).
 - ⇒ Grade III/IV encephalopathy.

Strongly consider transplantation if:

• Arterial lactate >3.5 mmol/L after early fluid resuscitation.

The criteria for transfer to a specialist liver unit are: (poor prognostic factors)

- Encephalopathy
- INR: >2.0 at < 48 hours, or > 3.5 at < 72 hours
 - ⇒ synthetic function (as determined by INR or PT) is the best indicator.
- Serum creatinine: >200 µmol/L
- Blood pH: <7.3
- Systolic BP: <80 mmHg.

Monitoring and endpoints for treatment

Hepatotoxicity

- In patients being treated with acetylcysteine for liver toxicity the acetylcysteine should be continued until the INR is 1.3 or less OR INR is falling towards normal on two consecutive blood tests, and less than 3.0.
- Blood tests (urea and electrolytes, creatinine, INR, and ALT) should be re-checked every 8
 to 16 hours to assess the progress of the hepatic injury. There is no clinical benefit in
 continuing treatment with acetylcysteine for a rise in ALT if the INR has normalised.

Time-sensitive treatment issues

- 8-hour window
 - ⇒ the need for acetylcysteine treatment should be based on a serum paracetamol concentration determined within this 8-hour window.
 - ⇒ acetylcysteine within 8 hours of an acute ingestion → prevent hepatic injury in nearly all patients
 - ⇒ Empiric acetylcysteine therapy should be initiated for patients who:
 - present later than 8 hours after ingestion;
 - when serum paracetamol concentrations cannot be determined within 8hours;

or if the exact timing of the ingestion is uncertain.

adverse effects

- oral acetylcysteine → nausea and vomiting.
- intravenous acetylcysteine → anaphylactoid reaction (e.g., nausea, flushing, vomiting, rash, urticaria, pruritus, angio-oedema, dyspnoea, wheezing, bronchospasm, tachycardia, and hypotension),
- Previous anaphylactoid reaction to acetylcysteine is not a contraindication to receiving acetylcysteine.
 - ⇒ Patients with a previous anaphylactoid reaction should be given an H1 and an H2 antagonist.
 - ⇒ Patients with previous bronchospasm reaction to acetylcysteine can be given nebulised salbutamol.
 - ⇒ Patients considered at risk of anaphylactoid reactions (e.g., those with atopy, bronchospasm, asthma, or a previous reaction) should be administered prophylactic medication such as antihistamines to reduce adverse reactions.
- Methionine is used as an oral antidote for paracetamol poisoning in those who cannot tolerate N-acetylcysteine

Paracetamol and smoking

- Enzyme induction with cigarette smoking does affect paracetamol metabolism. Its importance however, is in toxicity.
- Smokers would be classified as in a high risk for paracetamol overdose and are assessed using a different time - paracetamol level curve.

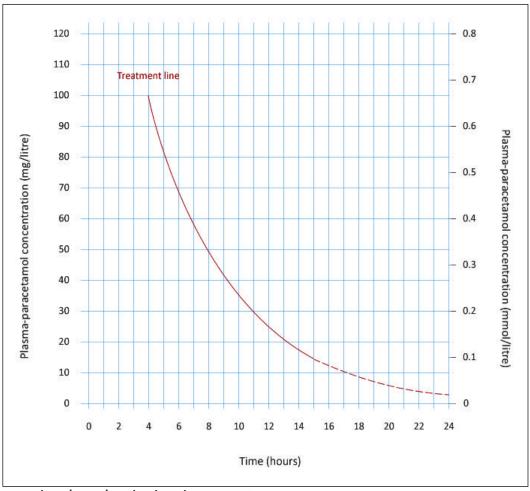
Complications

- Untreated paracetamol poisoning may cause varying degrees of liver injury over the 2 to 4 days following ingestion, including fulminant hepatic failure.
 - ⇒ Hepatotoxicity is extremely rare in patients treated with acetylcysteine within 8 hours of an acute paracetamol overdose.
- Lactic acidosis is recognised complication
- Hypoglycaemia is seen when paracetamol toxicity leads to significant impairment of hepatic synthetic function
 - ⇒ Severe hypoglycaemia affects 40% of patients with fulminant liver failure, which exacerbates encephalopathy.
- Paracetamol nephrotoxicity

 - can develop later than liver toxicity
 The mechanism of kidney injury is similar to that of the liver,
 - there is little evidence that N-acetyl cysteine confers any renal protection.
 - usually the renal function returns to baseline after a few weeks.
 - > Haemodialysis may be required to support the patient during the acute episode.

Prognosis

- The prognosis is poor in those with
 - ➤ Blood PH less than 7.0
 - Prolonged prothrombin time (more than 100s) and
 - Serum creatinine more than 300 uM.
 - Mortality is greater if the patient is more than 40 years of age.



paracetamol overdose treatment nomogram

Adult Dosage Table (Royal College of Emergency Medicine Guidance. http://www.rcem.ac.uk)

Regimen	First Infusion	Second Infusion	Third Infusion
Infusion fluid	200 mLs 5% glucose or sodium chloride 0.9%	500 mLs 5% glucose or sodium chloride 0.9%	1000 mLs 5% glucose or sodium chloride 0.9%
Duration of infusion	1 hour	4 hours	16 hours
Drug dose	150 mg/kg	50 mg/kg	100 mg/kg
	acetylcysteine	acetylcysteine	acetylcysteine

Although hepatotoxic in high doses even in fairly advanced chronic liver disease paracetamol can be used safely as long as doses do not exceed 2-3 g per day. The main exception to this is alcoholic liver disease where the patient continues to drink, in this setting induction of enzymes and depletion of glutathione increases the chances of hepatotoxicity.

Paraquat poisoning

Properties of Paraguat

- Paraquat is a very toxic compound
- As little as 2 g is potentially fatal (10 ml of a concentrated 20% solution)

Presentation

 Initial signs of toxicity are due to its corrosive effects on the gastrointestinal tract and oropharynx

Pathology

- Paraquat is rapidly absorbed and is sequestered in the lungs, where it reacts with oxygen to form hydrogen peroxide and superoxide anions
- Hydrogen peroxide and superoxide anions are responsible for cell death, which leads to an
 acute alveolitis

Prognosis

- Death tends to occur within hours to days in patients who have ingested more than 6 g of Paraguat
- Death tends to occur within days in those who have ingested 3-6 g of Paraquat
- Illness following ingestion of 1.5-3 g Paraquat follows a much more protracted course and delayed pulmonary
- fibrosis can lead to death up to 6 weeks after ingestion

Management

- · supportive care
- · activated charcoal to reduce absorption
- oxygen supplementation can increase pulmonary toxicity, by increasing the rate of hydrogen peroxide and superoxide anion production
- Measurement of plasma paraquat concentration can help in assessing prognosis and can aid treatment
- Plasma concentration measurements are also useful in the management of poisoning with paracetamol, salicylates, lithium, iron, methanol, ethylene glycol and theophylline

Organophosphate insecticide poisoning

Organophosphate is an anticholinesterase, thus prolonging the effects of acetylcholine.

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Organophosphates are rapidly absorbed through the gastrointestinal and respiratory tracts and the skin

Mechanism

- The principal action of organophosphates is inhibition of acetylcholinesterases
- This results in the accumulation of acetylcholine at muscarinic receptors, nicotinic receptors and in the central nervous system

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

Hypersalivation and miosis are the specific clues to acetycholine overactivity.

- Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

Presentation

The presentation relates to the sites of accumulation of acetylcholine

- · Accumulation at muscarinic receptors leads to:
 - miosis
 - hypersalivation
 - sweating
 - diarrhoea
 - excessive bronchial secretions
- Accumulation at nicotinic receptors leads to:
 - muscle fasciculations
 - > tremor
- · Accumulation in the central nervous system leads to:
 - anxiety
 - loss of memory
 - headache
 - coma
- Organophosphate-induced neuropathy starts to develop 2 weeks after exposure
 - Initial presentation of neuropathy is a flaccid paralysis
 - Later, hypertonia, hyperreflexia and a spastic paralysis occur

Management

- atropine
- the role of pralidoxime(an activator of cholinesterase) is still unclear meta-analyses to date have failed to show any clear benefit

Carbon Monoxide (CO) Poisoning



In carbon monoxide
poisoning, the patient's
oxygen saturation is usually
normal. This is because
carboxyhemoglobin is read
by the pulse oximeter as a
normal saturated hemoglobin
molecule.

Risk factors

 A hypoxemic poisoning syndrome seen in patients who have been exposed to automobile exhaust, smoke inhalation, barbecues, or old appliances in poorly ventilated locations.

Pathophysiology

• CO binds with high affinity to haemoglobin, forming carboxyhaemoglobin. CO also binds myoglobin and mitochondrial cytochrome oxidase.

Features

- Presents with hypoxemia, cherry-red skin (rare), confusion, and headaches. Coma or seizures occur in severe cases.
- Chronic low-level exposure may cause flu-like symptoms with generalized myalgias, nausea, and headaches. Ask about symptoms in others living in the same house.
- Suspect smoke inhalation in the presence of singed nose hairs, facial burns, hoarseness, wheezing, or carbonaceous sputum.
- CO poisoning causes tissue hypoxia, anaerobic metabolism and lactic acidosis.

Diagnosis

- Check an ABG and serum carboxyhemoglobin level (normal is < 5% in nonsmokers and < 10% in smokers).
- Check an ECG in the elderly and in patients with a history of cardiac disease.

Treatment

- 100% O2
- after which transfer to a centre with **hyperbaric oxygen** should be considered.
- Patients with airway burns or smoke inhalation may require early intubation, since upper airway edema can rapidly lead to complete obstruction.

Antiemetic

Antiemetics

- Aprepitant → is a neurokinin receptor blocker used in the prevention of chemotherapy induced nausea.
- Hyoscine → antiemetics functions as a cholinergic muscarinic antagonist
 - ➡ It acts as a competitive antagonist at muscarinic acetylcholine receptors; it is thus classified as an anticholinergic or as an antimuscarinic drug.
- Metoclopramide is a dopamine receptor antagonist that can induce parkinsonism. It can also
 worsen control in patients with idiopathic Parkinson's disease to its antagonistic effect on dopamine
 receptors.
- Domperidone is also a dopamine antagonist but acts peripherally.
 - ⇒ Best drug for nausea and vomiting associated with Parkinson treatment.
 - ⇒ Drugs such as apomorphine and bromocriptine cause vomiting through peripheral stimulation of the chemoreceptor trigger zone. Worsening of Parkinson's disease may result from the use of dopamine antagonists; however, domperidone is much less likely to cross the blood-brain barrier and is therefore the preferred agent in this case.
- Haloperidol: the main site of action for haloperidol with regards anti-emetic effects -->
 Chemoreceptor trigger zone
 - ⇒ Haloperidol is an anti-dopaminergic agent licensed for and used mainly as an anti-psychotic agent
 - ⇒ It does result in more extrapyramidal side-effects than phenothiazine-type agents, but is associated with less hypotension
- Phenothiazines (e.g. promethazine) and domperidone are also used as anti-emetic agents and act at the chemoreceptor trigger zone
- Cyclizine is an anticholinergic antihistamine acting through the vomiting centre.

Group	Drug	Antagonize d receptor	Mechanism	Specific features	Side effects
Dopamin e receptor antagoni sts/ proki	perazine	D ₂	Antiemetic effect at the area postrema	Antipsychotic agent Used in severe hyperemesis gravidarum	 Depression Fatigue Diarrhea Hyperprolactinemia Overdose leads to reversible extrapyramidal syndrome (e.g., dystonia, park insonism, tardive
netic agents	Domperi done		Antiemetic effect at the area postremaProkinetic effect	Prokinetic effect: to treat diabetic and post-surgery	
	Metoclo pramide		Antiemetic effect in the CNS and at the area postrema Prokinetic effect:↑ gastric contractions, duodenal and jejunal motility, resting tone of the lower esophageal sphincter and decreased pylorus sphincter activity allow food to pass quickly	gastroparesis (delayed gastric emptying) Used in severe hyperemes is gravidarum	dyskinesia, and akathisia) and neuroleptic malignant syndrome • Antidote: biperide n(anticholinergic agent) • Do not combine metoclopr amide with antipsyc hotics because of the increased risk of dyskinesia! • Domperidone may cause cardiac arrhythmias.
Serotoni n receptor antagoni sts	Ondans etron (Zofran®)	5-HT₃	 Central- acting antiemetic effect Peripheral inhibition of the intestinal tract's vagal nerve signals 	Chemotherapy and radiation- induced- vomiting and pos toperative nausea and vomiting (PONV)	*Headaches *Constipation or diarrhea *QT interval prolongation(torsades de pointes) *Increase in liver enzymes *Serotonin syndrome
Anticholi nergic Agents	Scopola mine	M_2	 Antiemetic effect at the area postrema Peripheral inhibition of the intestinal tract's vagal nerve signals 	Especially effective against motion sickness or vesti bular-inducednausea and vomiting	 Anticholinergic side effects: dry mouth, mydriasis, t achycardia, urinary retention Antidote: physostig mine(cholinesteras e inhibitor)
Antihista mines	Meclizin e, dimen hydrinat e, diphen hydramin e, doxyla mine, pr omethazi ne	H ₁	Antiemetic effect in the CNS	Strong sedative Used in hyperemesis gravidarum (also see "Drugs of choice in pregnancy" (antiemetics)	drowsiness and confusion Anticholinergic side effects: dry mouth, dilated pupils, blurred vision, reduced bowel sounds, and urinary retention) → antidote: physo stigmine

5-HT3 antagonists

- 5-HT3 antagonists are antiemetics used mainly in the management of chemotherapy related nausea.
- They mainly act in the chemoreceptor trigger zone area of the medulla oblongata.

Examples

- Ondansetron
 - - Ondansetron is the first line drug for chemotherapy related nausea and vomiting.
 - Its effects are on both **peripheral** and **central nerves**.
 - One part is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting center in the medulla oblongata,
 - the other is a blockage of serotonin receptors in the chemoreceptor trigger zone.
 - ⇒ Common side effects of ondansetron are headache, drowsiness, and dizziness.
- granisetron

Adverse effects

· constipation is common

Metoclopramide

Action

· D2 receptor antagonist

Indications

- · mainly used in the management of nausea.
- gastro-oesophageal reflux disease
- prokinetic action is useful in gastroparesis secondary to diabetic neuropathy
- often combined with analgesics for the treatment of migraine (migraine attacks result in gastroparesis, slowing the absorption of analgesics)

Adverse effects

- extrapyramidal effects: oculogyric crisis. This is particularly a problem in children and young adults, especially girls, usually subsides within 24 hours following cessation of treatment and can be **treated with procyclidine 5-10 mg i.m.** (antimuscarinic).
- hyperprolactinaemia
- · tardive dyskinesia

Acute dystonic-dyskinetic reactions

- Risk factors
 - ⇒ mostly occur in children and young adults
 - ⇒ about 70% of cases are female.
 - ⇒ It occurs more commonly when excess of the recommended dose of metoclopramide is administered.
- Time frame
 - ⇒ The effects <u>usually occur within 72</u> hours but have been reported to occur within 30 minutes of starting treatment.
- Features
 - ⇒ oculogyric crisis
 - ⇒ opisthotonus
 - ⇒ torticollis
 - ⇒ trismus,
 - ⇒ tetanus-like reactions.

- ⇒ A blue discolouration of the tongue has also been described.
- Treatment
 - ⇒ generally self-limiting,
 - ⇒ the reaction can be reversed by an anticholinergic such as **benzatropine** or **procyclidine** or an antihistamine such as diphenhydramine.

MRCPUK-part-2-march-218: A 21-year female presented with acute spasm of her neck after metoclopramide injection. What is the most appropriate intervention?

→ Procyclidine

Other drugs

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<u>Antihistamines</u>

- Antihistamines (H₁ inhibitors) are of value in the treatment of allergic rhinitis and urticaria.
- Sedation and headaches are the most common adverse effects of antihistamines
- First generation antihistamines (chlorpheriramine and diphenhydramine) are more sedating than the newer agents.

Sedating antihistamines

- Cyproheptadine
- Chlorpheniramine
 - ⇒ As well as being sedating these antihistamines have some antimuscarinic properties (e.g. urinary retention, dry mouth).

Non-sedating antihistamines

- loratidine
- cetirizine
- Desloratadine
 - ▶ is a long-acting H-1-receptor antagonist
 - has poor penetration into the central nervous system.
 - > does not interact with antibiotics or other co-administered medications
- Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.
- Of the newer antihistamines, cetirizine and levocetirizine are more sedating than loratadine and desloratadine, and possibly more sedating than fexofenadine.

Other notes

- Terfenadine (a pro-drug) has been associated with cardiac arrhythmias (torsades de pointes) especially in individuals with prolonged QT intervals.
 - Fexofenadine is the active metabolite of terfenadine and does not appear to have the same arrhythmogenic effects as terfenadine.
 - second-generation antihistamine
 - has fewer sedative and anticholinergic side effects.
 - in patients with allergy + history of narrow-angle glaucoma → Fexofenadine
 - first-generation antihistamines (eg: Chlorpheniramine) have anticholinergic side effects that can cause mydriasis and trigger an acute attack in patients with a history of narrow-angle glaucoma,
- Cetirizine, desloratadine and fexofenadine are prescribed for allergic rhinitis (hay fever) and

- all three are equally effective
- · cetirizine and fexofenadine interact with erythromycin and other macrolides
- Chlorphenamine maleate and terfenadine cause drowsiness and also interact with erythromycin

Human and animal bite

- Co-amoxiclav is recommended as first-line treatment for all cat or human bites and other complicated animal bites.
- In patients who are pencillin allergic, doxycycline plus metronidazole is a typical first choice regimen.
- Only 15 20% of dog bites become infected, and providing the wound is appropriately cleaned and not considered at risk (for example, crush or deep wounds) then antibiotic prophylaxis may not be required.

Botox → Paralysis of frontalis → eyebrows are drooping (eyebrow ptosis).

- Botox (onabotulinumtoxinA) is an injectable neuro-toxin used for the treatment of chronic migraines, limb spasticity, axillary hyperhidrosis, cervical dystonia, strabismus, and blepharospasm.
- Botox is a neurotoxin derived from the bacteria, Clostridium botulinum. It blocks neuromuscular
 transmission inhibition of acetylcholine release at the presynaptic membrane. The end result is that
 the muscle contraction is inhibited.
- The action of Botox is not permanent because collateral axonal sprouting establishes new neuromuscular junctions, restoring muscle function.
- Frontalis is a quadrilateral muscle found on the forehead that elevates the eyebrows; hence paralysis of this muscle can lead to eyebrow ptosis.

D-Penicillamine

- used to reduce the body copper in Wilson's disease & as a chelating agent in lead poisoning
- D-Penicillamine is associated with → pancytopenia and tubulointerstitial nephritis

Isotretinoin

Isotretinoin adverse effects

- teratogenicity females MUST be taking contraception
- low mood
- dry eyes and lips
- raised triglycerides
- hair thinning
- nose bleeds
- Isotretinoin is an oral retinoid used in the treatment of severe acne.
- Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin

Adverse effects

- Teratogenicity: \$\text{\text{\text{\$}}} \text{ MUST} be using two forms of contraception (e.g. COCP and condoms).
 - > Women must have a negative pregnancy test before treatment
 - and be on effective contraception for at least a month before the course begins, during the course and for a month after it finishes

- > Congenital deafness, CNS and heart defects may occur in children exposed to isotretinoin in utero
- Dry skin, eyes and lips: the most common side-effect of isotretinoin
- · Low mood, depression
- Raised triglycerides
- Hair thinning
- Nose bleeds (caused by dryness of the nasal mucosa)
- Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason

Cinnarizine

- Cinnarizine is thought to be particularly useful for the treatment of motion sickness as it has a dual action:
 - it acts as a depressant of the vestibular system
 - it dampens down smooth muscle contraction in the gut

Ergotamine

- Ergotamine is an old drug and a member of the family of ergot alkaloids.
- It is licensed as a treatment and prophylaxis for migraines but has been largely superseded by newer agents despite its efficacy, cost and relatively benign side effect profile.
- A derivative of the drug, ergometrine, is used in obstetrics to reduce the incidence of post partum haemorrhage.
- Ergotamine, like all ergot alkaloids, is a potent vasoconstrictor which is partly how it exerts its clinical effects, however in overdosage it can cause significant peripheral vasoconstriction causing critical ischaemia and gangrene. Coronary vasoconstriction may occur, with or without flow limiting lesions causing cardiac ischaemia which may be manifest as chest pain, arrhythmia or even sudden death.
- Contraindications to the use of ergotamine are flow limiting coronary lesions or peripheral vascular disease.
- Additionally, ergotamine has a complex series of effects on central nervous neurotransmitter systems including serotonergic, dopaminergic and noradrenergic systems which can cause excitement, confusion, paranoia, visual and auditory hallucinations and delusions in overdose.
- It is also a metabolic precursor to the highly hallucinogenic chemical lysergic acid diethylamide (LSD) which inactivates 5-HT2A receptors in the brain.
- At normal doses, side effects of ergotamine are relatively minor and unlikely to cause significant clinical signs in the absence of underlying pathology. However, metabolism of ergot alkaloids is predominantly by the hepatic enzyme CYP3A4 which is almost totally inhibited by macrolide antibiotics. Co-administration of ergotamine and clarithromycin may be expected to produce a rapid picture of ergotism with confusion, psychosis, muscle cramps, seizures, peripheral and coronary vasospasm, severe headache and gastrointestinal symptoms of bowel ischaemia, cramps, diarrhoea and GI haemorrhage. Myocardial infarction, renal infarction, stroke and critical limb ischaemia may occur if not treated.
- Interestingly, ergot alkaloid derivatives are naturally produced by the fungus Claviceps purpurea which may infect crops.
- Historically, significant outbreaks of ergotism have been seen due to ingestion of crops contaminated with ergot and there is some historical evidence that claims of witchcraft are ascribable to the psychosis of ergot poisoning.

Finasteride

Finasteride treatment of BPH may take 6 months before results are seen

- Finasteride is an inhibitor of 5 alpha-reductase.
- 5-α-Reductase converts testosterone to dihydrotestosterone (DHT)
- . DHT is much more active than testosterone and binds more avidly to cytoplasmic receptors
- DHT stimulates prostate growth and may be responsible for benign prostatic hyperplasia in the elderly

Indications

- · benign prostatic hyperplasia
- male-pattern baldness

Adverse effects

- impotence
- decrease libido
- ejaculation disorders
- gynaecomastia and breast tenderness

Finasteride causes decreased levels of serum prostate specific antigen

Acetazolamide

Action

- carbonic anhydrase inhibitor, hence causing the accumulation of carbonic acid
- Inhibits proximal tubule bicarbonate reabsorption in a similar fashion to type-2 renal tubular acidosis (RTA) → associated with metabolic acidosis
- By excreting bicarbonate, the blood becomes acidic, causing compensatory hyperventilation with deep respiration (Kussmaul respiration), increasing levels of oxygen and decreasing levels of carbon dioxide in the blood. Hence used in treatment of high altitude sickness.

Indications

- intracranial hypertension
 - > post-haemorrhagic hydrocephalus (often with furosemide)
 - > primary idiopathic pseudotumour cerebri (benign intracranial hypertension)
- · reducing intraocular pressure
- prevent acute mountain sickness
- preventative agent for contrast nephropathy

Side effects

- metabolic acidosis, due to bicarbonate loss in the proximal and distal tubules through inhibition of reabsorption
 - hyperchloraemic, normal anion gap metabolic acidosis.
- Hypokalaemia
- Acute interstitial nephritis (AIN)
- Agranulocytosis and thrombocytopenia
- hyponatremia,
- hyperglycemia, hypoglycemia, glycosuria,
- crystalluria (and hematuria), and polyuria.
- peripheral paresthesiae

carbonic anhydrase works to control the equilibrium between carbon dioxide and carbonic acid in order to maintain proper blood pH. Through which mechanism does **carbonic anhydrase** exert its influence on reaction kinetics?

→ Lowers the activation energy

- Enzymes like **carbonic anhydrase** lower the energy of activation that is needed to initiate a reaction.
 - Inhibition of carbonic anhydrase prevents the conversion of carbon dioxide (CO₂) and water (H₂O) to carbonic acid (H₂O₃) thus affecting the blood pH.

Bicarbonate therapy

- Can increase extracellular pH only if the carbon dioxide (CO₂) produced can be removed by adequate ventilation.
- Indeed, if hypercapnia occurs then as CO₂ crosses cell membranes easily, intracellular pH may
 decrease even further with further deterioration of cellular function.
- Bicarbonate has a negative inotropic effect,
- reducing cerebral blood flow;
- It shifts the oxygen dissociation curve to the left, inhibiting oxygen release to tissues.
- · Exacerbates intracellular acidosis in cardiorespiratory arrest

Bisphosphonates

Bisphosphonates inhibit osteoclasts

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone. They **inhibit osteoclasts** by reducing recruitment and promoting apoptosis.

The mechanism of action of bisphosphonates involves the inhibition of farnesyl diphosphate synthase within osteoclasts. In doing this they interfere with geranylgeranylation (attachment of the lipid to regulatory proteins), which causes osteoclast inactivation. This leads to reduced bone turnover, increased bone mass and improved mineralisation.

Clinical uses

- · prevention and treatment of osteoporosis
 - Bisphosphonates licensed for the prevention and treatment of osteoporosis include alendronate, risedronate and ibandronate.
- hypercalcaemia
- Paget's disease
- pain from bone metastases
 - The bisphosphonates zoledronate and pamidronate are used for the treatment of metastatic bone disease and short term management of hypercalcaemia.

Adverse effects

Bisphosphonates can cause a variety of oesophageal problems

- oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate)
- osteonecrosis of the jaw:
 - This is a consequence of potent anti-resorptive action of the nitrogen containing bisphosphonates.
 - Most cases have been associated with zoledronic acid and pamidronate given intravenously for metastatic bone disease.
 - The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
 - > Dental disease is a recognised predisposing factor.
 - ➤ The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.
- Bisphosphonate infusions can lead to hypocalcaemia although it is more common when using larger doses in malignancy induced hypercalcaemia as oppose to the smaller dose used in osteoporosis.
- increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate The BNF suggests the following counselling for patients taking oral bisphosphonates
 - 'Tablets should be swallowed whole with plenty of water while sitting or standing; to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication); patient should stand or sit upright for at least 30 minutes after taking tablet'

Botulinum toxin

As well as the well publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed **indications:**

- blepharospasm
- · hemifacial spasm
- · focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
- spasmodic torticollis
- · severe hyperhidrosis of the axillae
- achalasia

Immunoglobulins: Therapeutics

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008 **Uses**

- · Primary and secondary immunodeficiency
- Idiopathic thrombocytopenic purpura (ITP)
- · Myasthenia gravis
- · Guillain-Barre syndrome
- Kawasaki disease
- Toxic epidermal necrolysis (TEN)
- Pneumonitis induced by CMV following transplantation
- Low serum IgG levels following hematopoietic stem cell transplant for malignancy
- Dermatomyositis
- Chronic inflammatory demyelinating polyradiculopathy

Basics

- Formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- Half-life of 3 weeks

Malignant hyperthermia (MH)

Overview

- · condition often seen following administration of anaesthetic agents
- characterised by increased temperature and muscle rigidity during anaesthesia, which results from abnormal skeletal muscle contraction and increased metabolism.
- · caused by excessive release of Ca2+ from the sarcoplasmic reticulum of skeletal muscle
- associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls Ca2+ release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

Causative agents

- halothane (volatile anaesthetic agents)
- suxamethonium
- other drugs: antipsychotics (neuroleptic malignant syndrome)

Investigations

- Serum creatine kinase(CK) elevation and myoglobinuria are suggestive but not diagnostic of MH.(both known to increase after giving suxamethonium to normal patients)
- Contracture tests with halothane and caffeine are the investigations of choice.
- Muscle biopsies may appear histologically normal.

Management

- dantrolene prevents Ca2+ release from the sarcoplasmic reticulum
 - ⇒ Intravenous dantrolene (up to 10 mg/kg) is the only available specific treatment
 - ⇒ Care must be taken when administering as the solution has a pH of 9-10.

Prognosis

 The prognosis of malignant hyperpyrexia is good when the appropriate treatment is instigated early, mortality being less than 5% (prior to dantrolene the mortality was 80%).

Intravenous fluid therapy

Composition of electrolytes in commonly used crystalloids

Content	Plasma	Sodium chloride 0.9%*	Sodium chloride 0.18%/ 4% glucose(a)	0.45% NaCl/ 4% glucose(a)	5% glucose(a)	Hartmann'	Lactated Ringer's (USP)	Ringer's acetate
Na ⁺ (mmol/l)	135-145	154	31	77	0	131	130	130
Cl ⁻ (mmol/l)	95-105	154	31	77	0	111	109	112
[Na [†]]:[Cl¯] ratio	1.28 - 1.45:1	1:1	1:1	1:1	-	1.18:1	1.19:1	1.16:1
K ⁺ (mmol/l)	3.5-5.3	*	*	*	*	5	4	5
HCO3 ⁻ / Bicarbonate	24-32	0	0	0	0	29 (lactate)	28 (lactate)	27 (acetate)
Ca ²⁺ (mmol/l)	2.2-2.6	0	0	0	0	2	1.4	1
Mg ²⁺ (mmol/l)	0.8-1.2	0		0		0	0	1
Glucose (mmol/ I)	3.5-5.5	0	222(40 g)	222 (40g)	278(50 g)	0	0	0
pН	7.35-7.45	4.5-7.0	4.5		3.5-5.5	5.0-7.0	6-7.5	6-8
Osmolarity (mOsm/l)	275-295	308	284		278	278	273	276

Intravenous fluid therapy in adults in hospital (NICE guidelines 2013)

- · Indicators for urgent fluid resuscitation:
 - systolic blood pressure is less than 100 mmHg
 - > heart rate is more than 90 beats per minute
 - > capillary refill time is more than 2 seconds or peripheries are cold to touch
 - respiratory rate is more than 20 breaths per minute
 - ➤ National Early Warning Score (NEWS) is 5 or more
 - passive leg raising suggests fluid responsiveness
- Resuscitation
- If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130– 154 mmol/l, with a bolus of 500 ml over less than 15 minutes.
- Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis.
- Routine maintenance
- If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:
- 25–30 ml/kg/day of water and
- approximately 1 mmol/kg/day of potassium, sodium and chloride and
- approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs)
 (patients rarely need more than a total of 3 litres of fluid per day)
- Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who:
- are older or frail
- · have renal impairment or cardiac failure
- are malnourished and at risk of refeeding syndrome
- →When prescribing for routine maintenance alone, consider using 25–30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1.
- Prescribing more than 2.5 litres per day increases the risk of hyponatraemia. These are initial prescriptions and further prescriptions should be guided by monitoring.
- → Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and wellbeing.

British Consensus Guidelines on Intravenous Fluid Therapy (2011) Recommendation

- Because of the risk of inducing hyperchloraemic acidosis in routine practice, when
 crystalloid resuscitation or replacement is indicated, balanced salt solutions e.g. Ringer's
 lactate/acetate or Hartmann's solution should replace 0.9% saline, except in cases of
 hypochloraemia e.g. from vomiting or gastric drainage.
- Hypochloraemia is an indication for the use of 0.9% saline, with sufficient additions of potassium and care not to produce sodium overload.
- Losses from diarrhoea/ileostomy/small bowel fistula/ileus/obstruction should be replaced volume for volume with Hartmann's or Ringer-Lactate/acetate type solutions.
- "Saline depletion," for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's.

Daily requirement

- The typical daily requirement is:
 - ⇒ 1.5 ml/kg/hr fluid for a 80kg man around 2-3 litres/day
 - ⇒ 70-150mmol sodium
 - ⇒ 40-70mmol potassium
- This is why the typical regime prescribed for patients is:

- ⇒ 1 litre 5% dextrose with 20mmol potassium over 8 hours
- ⇒ 1 litre 0.9% normal saline with 20mmol potassium over 8 hours

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

	Na⁺	CI ⁻	K ⁺	HCO3	Ca ²⁺
Plasma	135-145	98-105	3.5-5	22-28	2.3-2.6
0.9% normal saline	150	150	-	-	-
5% dextrose	-	-	-	-	-
Hartmann's solution	131	111	5	29	2

Normal saline has a pH of 5 and may produce a mild metabolic acidosis with significant infusions.

Which fluid would be the most appropriate to replace the fluid being lost in a patient with a paralytic ileus draining 2 litres of fluid a day through a nasogastric tube?

- → 0.9% sodium chloride with potassium according to electrolytes
 - it is essential to supply sufficient chloride ions to replace the chloride being lost in the gastric fluid (gastric juice is essentially dilute hydrochloric acid).

Lactulose

- Lactulose MOA → Osmotic laxative
- Causes hypomagnesaemia associated with diarrhoea
- Is not absorbed.
- Does not affect the absorption of spironolactone and
- · May be used in diabetics.
- It reduces proliferation of ammonia producing bacteria

It is used in patients with cirrhosis/hepatic encephalopathy to limit the proliferation of ammonia-forming gut organisms and increase the clearance of protein load in the gut.

- lactulose broken down by colonic bacteria → production of lactic acid and other organic acids → contents of the gut become more acidic (↓ PH) → ↓↓ absorption of ammonia → ↑↑ ammonia in the gut → ↑↑ water drawn into the lower bowel
- laxative abuse

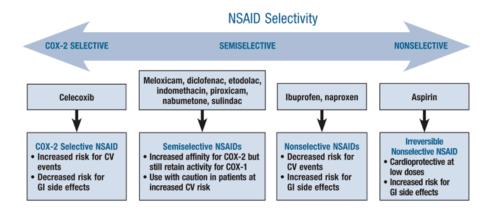
Features

- most commonly seen in young female patients complaining of chronic diarrhoea.
 - ⇒ The diarrhoea is frequently high volume
- underweight girl with calluses on her knuckles may point towards induced vomiting and a diagnosis of bulimia, which would fit with possible laxative abuse.
- Hvpokalaemia
 - Due to increased GI potassium loss
 - > symptoms of fatigue which are consistent with hypokalaemia.
 - GI loss leads to renal conservation of potassium, a urinary concentration of potassium of less than 1 mmol/l being highly suggestive of laxative abuse.

Bismuth

- subsalicylate is a colloidal substance frequently included in over-the-counter treatments for gastrointestinal discomfort.
- It has anti-secretory, anti-inflammatory, and antibacterial properties.
- It may be included in multidrug regimens against H. pylori.
- Its most unique side-effect is the appearance of black stool or a black tongue, both secondary to the drug's interaction with sulfur.

Non-steroidal anti-inflammatory drugs (NSAID)



Non-steroidal anti-inflammatory drugs (Nice 2015)

- If an NSAID is needed, use ibuprofen (1200 mg a day or less) or naproxen (1000 mg a day or less).
- Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.
- Co-prescribe gastroprotective treatment (a proton pump inhibitor) with NSAIDs
- In October 2012, a European Medicines Agency (EMA) review on the cardiovascular safety
 of NSAIDs confirmed that diclofenac is associated with cardiovascular risks that are higher
 than ibuprofen and naproxen, and similar to the COX-2 inhibitors.
- etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHa
- the arterial thrombotic risk with diclofenac is similar to that of COX-2 inhibitors.
- diclofenac is now contraindicated in patients with established:
 - > ischaemic heart disease
 - peripheral arterial disease
 - cerebrovascular disease
 - congestive heart failure (New York Heart Association [NYHA] classification II–IV)

Indometacin → is an inhibitor of both prostaglandin synthase and lipoxygenase enzymes

Side effects

- Current evidence suggests that naproxen, a nonselective NSAID, is associated with the lowest risk of cardiovascular events. Therefore, naproxen is the NSAID of choice in patients with high cardiovascular risk.
- Optic neuritis is described as being rarely associated with diclofenac therapy.

- A range of other CNS side effects has also been noted on the summary of product characteristics, these include headache, dizziness, vertigo and in rare circumstances drowsiness.
- gastrointestinal bleeding occurs <u>due to</u> depletion of mucosal prostaglandin E (PGE) levels
- Endoscopic evidence of peptic ulceration is found in 20% of NSAID users even in the absence of symptoms
- The relative risk of causing GI bleeds differs with different preparations:
 - ibuprofen has a low risk
 - piroxicam and azapropazone have the highest risk
- While all NSAIDs may contribute to anaemia, usually via gastrointestinal bleeding, mefenamic acid is particularly associated with immune haemolytic anaemia.
- NSAIDs reduce glomerular perfusion by <u>inhibiting production of prostaglandins</u> which
 dilate the <u>afferent arteriole</u> of the glomerulus. The reduction in blood supply to the kidney
 results in impairment of kidney function.
- NSAIDs can also cause an interstitial nephritis but this is often accompanied by a nephrotic syndrome-like picture.

Non-steroidal anti-inflammatory drugs are contraindicated in chronic liver disease for a variety of reasons:

- their gastrointestinal side effects increase the risk of bleeding, particularly in those with varices.
- Additionally, due to systemic vasodilatation renal circulation is very dependent upon
 prostaglandin production to maintain glomerular filtration. Inhibition of this mechanism by
 non-steroidals, in addition to their other nephrotoxic effects, means that their use in patients
 with chronic liver disease, especially where there is pre-existing renal impairment, can
 precipitate renal failure.

Overdose with (NSAIDs)

Presentation and aetiology

- GIT upset (epigastric tenderness, nausea, vomiting and diarrhea) These effects are mainly due to the inhibition of cyclo-oxygenase
- \rightarrow convulsions (10-20%) \rightarrow more common in mefenamic acid over dose

Large overdoses can present with:

- acidosis
- > renal impairment
- gastrointestinal haemorrhage
- > CNS effects (drowsiness, coma, cerebellar signs)

Management

- > Activated charcoal in patients presenting within the first hour
- Supportive care
- Oral H2-histamine blockers and proton-pump inhibitors may reduce the symptoms of gastrointestinal toxicity

Celecoxib (COX)-2 inhibitor)

Celecoxib is an NSAID that is safe to use in patients with gastritis or gastric ulcers as it does not affect COX1 action at the stomach.

Cox-2 inhibitors have a much lower risk of gastrointestinal bleed and high risk of cardiovascular events, they should not be prescribed to those with cardiovascular disease, or in those with high risk of cardiovascular disease.

Action

- Celecoxib is a selective cyclo-oxygenase(COX)-2 inhibitor
 - differing from the other non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen which affects both COX-1 and COX-2.
 - COX-1 is involved in platelet aggregation and inhibition of this by the NSAIDs produces its beneficial cardiovascular effects.
 - platelet aggregation is not affected by COX-2.
 - Celecoxib has a lower level of anti-platelet activity than naproxen

Advantages

- Naproxen and celecoxib have been shown to be as effective at reducing inflammation.
- One of the benefits of celecoxib is its reduced incidence of upper gastrointestinal side effects.

Side effects

- As with the non-specific NSAIDS, <u>hepatotoxicity</u> may occur with the COX-2 specific
 inhibitors resulting in cholestatic, hepatocellular or mixed liver injury. Rates seem to be
 comparable between the traditional NSAIDs and the COX-2 selective inhibitors.
- The <u>cardiovascular effects</u> of the COX-2 inhibitors remains under study, and care should be taken before prescribing them to patients with a past medical history of significant cardiovascular disease.
- Rofecoxib (Vioxx) has been withdrawn due to its increased cardiovascular events compared with naproxen.
- What is the mechanism of celecoxib-induced deterioration in renal function?
 - inhibition of afferent arteriole vasodilatation

Interaction

• Co-administration of diuretics and COX-2 inhibitors should be avoided if possible, as COX-2 inhibitors may reduce the antihypertensive and diuretic effects of diuretics. This may be due to impaired prostaglandin synthesis, which results in salt and water retention. In addition, COX-2 inhibitors have nephrotoxic effects which can be exacerbated by diuretics.

Aminosalicylate drugs

- 5-aminosalicyclic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an antiinflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis
- The safety of the 5-aminosalicylic acid (5-ASA) drugs in pregnancy is best supported by the data on Salazopyrin which have been available for the longest.

Sulphasalazine

- a combination of sulphapyridine (a sulphonamide) and 5-ASA
- many side-effects are due to the sulphapyridine moiety: rashes, oligospermia, headache, Heinz body anaemia, megaloblastic anaemia
- other side-effects are common to 5-ASA drugs (see mesalazine)

Mesalazine

- a delayed release form of 5-ASA
- sulphapyridine side-effects seen in patients taking sulphasalazine are avoided
- side-effects: Gl upset, headache, agranulocytosis, pancreatitis, interstitial nephritis
 - pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Olsalazine

two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

Anti-TNF therapy (NICE January 2016)

TNF-α inhibitors may reactivate TB

Drugs

- adalimumab, Golimumab, infliximab, certolizumab, tocilizumab
- · etanercept,

Action

• tumour necrosis factor alpha (TNF-α) inhibitors

Indications

- Refractory Crohn's disease.
- rheumatoid arthritis: for adults who have both the following characteristics:
 - Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
 - ➤ Have undergone <u>trials of two disease-modifying anti-rheumatic drugs (DMARDs)</u>, including methotrexate (unless contraindicated).
 - A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
 - Use of the TNF-α inhibitors for rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
 - > Follow up
 - Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.
 - monitored 6-monthly
 - withdraw treatment if a moderate EULAR response is not maintained.

Plaque psoriasis

- > Adalimumab is recommended for adults with plaque psoriasis only if:
 - condition is severe and
 - not improved with other treatments such as ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments.
 - > Follow up
 - Adalimumab treatment should be continued beyond 16 weeks only if the psoriasis has clearly improved within this time.

· ankylosing spondylitis

- NICE states that adalimumab, etanercept and golimumab may be used for ankylosing spondylitis (AS) only if:
 - treatment with two or more NSAIDs for four weeks at the highest possible dose has not controlled the symptoms
 - confirms that condition has not improved by 2 methods:
 - 1) level of **pain is assessed twice** (using a simple scale to fill in) 12 weeks apart and confirms that condition has **not improved**
 - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is tested twice, 12 weeks apart, and confirms that condition has not improved
 - ➡ BASDAI is a set of measures to evaluate condition, by asking a number of questions about symptoms

Side effects

- Reactions
 - Injection site reactions
 - Cutaneous reactions, including psoriasis
 - Infusion reactions
 - Infusion reactions with infliximab are classified as one of two types:
 - ❖ Acute reactions : occur within 24 hours.
 - ❖ Delayed reactions: develop between 1 and 14 days
- Neutropenia
- Infections
 - > risk of reactivation of tuberculosis or new infection
 - including miliary TB and some unusual extra-pulmonary TB
 - If patient had previous active TB, the optimal TB screening test in this situation→ Interferon gamma release assay
- Demyelinating disease → exacerbation of neurologic disorders associated with demyelination, such as multiple sclerosis.
- · Heart failure
 - ➤ Given the evidence to date, patients with symptomatic HF should be treated with strategies other than TNF-alpha inhibitors.
 - > In a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected.
- Malignancy
- Induction of autoimmunity

Usage

- Prior to initiating a TNF-alpha inhibitor, all patients should be screened for:
 - > tuberculosis.
 - hepatitis B, and
 - hepatitis C.
- All forms of anti-TNF therapy are given by injection.
 - > Etanercept is given as subcutaneous injection twice per week.
 - > Infliximab is given as an infusion (intravenous).
 - requires intravenous infusion in a hospital setting.
 - It is given 2-4 weekly initially and then on a 6-8 weekly basis and as per protocol.
 - Infliximab monotherapy induces the production of anti-infliximab antibodies, which may reduce its effectiveness. Adding methotrexate to infliximab therapy may prevent this response.
 - Adalimumab is given as (subcutaneous injection) on alternate weeks (every second week).
- Unlike methotrexate.
 - > there is little problem with nausea.
 - Nor is there the same concern for effects on blood cells and the liver which means less blood tests are required.
- TNF-α inhibitors should normally be used in combination with methotrexate.
 - ➤ If methotrexate is intolerant, adalimumab and etanercept may be given as monotherapy.

Monoclonal antibodies

Rituximab - monoclonal antibody against CD20

Cetuximab - monoclonal antibody against the epidermal growth factor receptor

Trastuzumab (Herceptin) - monoclonal antibody that acts on the HER2/neu receptor

Overview

- manufactured by a technique called somatic cell hybridization.
- This involves the fusion of myeloma cells with spleen cells from a mouse that has been
 immunized with the desired antigen. The resulting fused cells are termed a hybridoma and
 act as a 'factory' for producing monoclonal antibodies.
- The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse body with the constant region from an human antibody.

Some monoclonal antibodies in clinical use include:

monoclonal antibodies	Action	Indication
Digibind	Digoxin-binding antibody	for treatment of overdoses
		(increases clearance).
Abciximab	Glycoprotein Ilb,IIIa receptor	for unstable angina.
Pexelizumab	Anti-C5 (complement) - anti-	reduces myocardial
	inflammatory	infarction and death
		following coronary artery
		bypass graft (CABG) and
		angioplasty.
Rituximab	Anti-CD20	non-Hodgkin's lymphoma
Inf liximab	anti- TNF	rheumatoid arthritis and
		Crohn's
Cetuximab	anti-epidermal growth factor	metastatic colorectal cancer
	receptor	and head and neck cancer
Trast uzumab	anti-HER2, anti EGF receptor	metastatic breast cancer
Alemtuzumab	anti-CD52	chronic lymphocytic leukemia
Abciximab	anti-glycoprotein Ilb/Illa	undergoing PCI, prevention of
	receptor	ischemic events in patients
OKT3	anti-CD3	prevent organ rejection
Tocilizumab	directed against IL-6 receptor	treatment of moderate-to-
		severe RA in patients with an
		inadequate response to
		DMARDs and/or anti-TNF
Nivolumab	PD-1 (programmed cell	carcinoma of the lung
	death) inhibitor (PD-1	Nivolumab in combination with
	receptors are found on the	ipilimumab used in metastatic
	surface of T cells.)	melanoma and lymphoma.

Monoclonal Antibodies in Rheumatoid Arthritis

Monoclonal Antibodies Directed Against TNF-α	Antibodies Against B Cells	Antibodies That Interfere With IL-6 Function	Antibodies That Interfere With IL-1 Function
Infliximab Adalimumab	Rituximab	Tocilizumab	Anakinra
Golimumab Certolizumab			

Monoclonal antibodies are also used for:

- medical imaging when combined with a radioisotope
- identification of cell surface markers in biopsied tissue
- · diagnosis of viral infections

Side effects

Nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) are checkpoint inhibitors
which are used in the treatment of metastatic melanoma. Effects on the endocrine
system are being increasingly reported with prolonged therapy (hypophysitis and
hypothyroidism) and therefore it is important to assess patients carefully who present with
symptoms of hypothyroidism whilst on these drugs.

Abatacept

- What is the mechanism of action of abatacept?
 - Chimeric protein that inhibits T-lymphocyte activation
 - CTLA4 homologue
 - Abatacept is a cytotoxic lymphocyte antigen 4 (CTLA 4) homologue –
- Indication
 - licensed for RA treatment.

Proton pump inhibitors

- The proton pump is only contained in the tubo-vesicles of the parietal cell → secrete acid.
- Proton-pump inhibitors (e.g omeprazole) binds to gastric K+/H+-ATPase proton pump irreversibly
- However, as the half-life of the pump is 24-36 hours, the duration of the effect of protonpump inhibitors is limited by the degradation of these pumps.

Sildenafil

Viagra? - contraindicated by nitrates and nicorandil

Action

- Sildenafil is a phosphodiesterase type V inhibitor (PDE-5 inhibitors) used in the treatment of impotence.
- It increases intracavernosal cGMP levels, thereby competitively inhibiting the PDE-5 enzyme, and allowing nitric oxide-induced vasodilation.
 - it blocks cGMP phosphodiesterase, which is normally responsible for the breakdown of cGMP. Sildenafil therefore leads to increased levels of cGMP, which has vasodilatory effects to relax smooth muscle.

Contraindications

- patients taking nitrates and related drugs such as nicorandil
- hypotension
- recent stroke or myocardial infarction (NICE recommend waiting 6 months)
- · non-arteritic anterior ischaemic optic neuropathy

Side-effects

- visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic neuropathy Sildenafil is a PDE-5 inhibitor, but at high doses it also inhibits PDE-6, which leads to blue discoloration of vision. This can often be managed by reducing the dose of Sildenafil.
- nasal congestion
- flushing
- gastrointestinal side-effects
- headache

Anaesthetic drugs

halothane hepatitis (medical-masterclass.com 2017 mrcp part 2)

There are many causes of post-operative jaundice, but the fact that the surgery was
uncomplicated, the time course, the presence of joint / muscle pains and an
eosinophilia, all suggest halothane hepatitis as the most likely diagnosis. This is
thought to result as a hypersensitivity reaction. Treatment is supportive.

Effects on the liver

- Halothane
 - ⇒ Halothane undergoes ~25% metabolism by oxidative phosphorylation via hepatic cytochrome P450 systems.
 - ⇒ The major metabolite is trifluoroacetic acid (TFA), which is protein-bound and this TFA–protein complex can induce a T-cell-mediated immune response resulting in hepatitis ranging from mild transaminitis to fulminant hepatic necrosis and possibly death.
 - ⇒ the risk of fatal hepatic necrosis → one in 10 000 anaesthetics.
 - ⇒ Adult females are more commonly affected.
 - ⇒ Repeated exposure increases the risk of hepatitis.
 - ⇒ Halothane and hepatitis
 - Halothane can cause a mild liver dysfunction in approximately 30% of patients, due to the binding of reactive halothane metabolites to hepatocytes
 - Halothane oxidation by cytochrome P450 enzymes leads to the synthesis of trifluoroacetyl chloride, which covalently binds to hepatic molecules and causes an immune reaction Fulminant hepatitis results from the reactive metabolite, trifluoroacetyl chloride
 - Further exposure to halothane anaesthesia may lead to a fulminant hepatitis, where the mortality is approximately 90%.
 - Halothane induced hepatitis typically occurs five to seven days after exposure
- Less commonly hepatitis has been described after exposure to enflurane > isoflurane > desflurane.
- Sevoflurane is not metabolized to antigenic TFA-protein complexes.

Inhaled anaesthetic-like agent

- If patient was markedly comatose on arrival but quickly regains consciousness. This suggests a short acting (probably) inhaled anaesthetic-like agent → e.g Inhaled solvent glue.
- The inhaled solvents, due to their lipophilicity, are rapidly absorbed through the lungs and then
 quickly distributed to the brain and other organs. The effects therefore appear within minutes of
 inhalation.
- Typical substances that are inhaled include toluene, aromatic hydrocarbons and butane.

Pseudocholinesterase deficiency

Overview

- Pseudocholinesterase is a glycoprotein enzyme, produced by the liver.
- It specifically hydrolyzes exogenous choline esters.
- · most common in European; rare in Asians.
- Pseudocholinesterase deficiency results in delayed metabolism of the following:
 - Succinylcholine. depolarizing neuromuscular blocking agent (the most clinically important drug)
 - Suxamethonium is a depolarising neuromuscular blocking agent.

metabolised by plasma pseudocholinesterases.

- Approximately 1 in 2500 individuals have deficiency of this enzyme, resulting in prolonged neuromuscular blockade if they are given suxamethonium.
- 2. mivacurium.
- 3. procaine.
- 4. cocaine.
- After an intravenous dose of succinylcholine in individuals with normal plasma levels of normally functioning pseudocholinesterase enzyme:
 - ⇒ hydrolysis and inactivation of 90-95% of i.v succinylcholine occurs before it reaches the neuromuscular junction.
 - ⇒ The remaining 5-10% of the dose acts as an acetylcholine receptor agonist at the neuromuscular junction, causing prolonged depolarization of the postsynaptic junction of the motor-end plate.
 - ⇒ This depolarization initially triggers fasciculation of skeletal muscle.
 - ⇒ As a result of prolonged depolarization, endogenous acetylcholine released from the presynaptic membrane of the motor neuron does not produce any additional change in membrane potential after binding to its receptor on the myocyte.
 - ⇒ Flaccid paralysis of skeletal muscles develops within 1 minute.
- In normal subjects, skeletal muscle function returns to normal approximately 5 minutes after a single bolus injection of succinylcholine as it passively diffuses away from the neuromuscular junction.
- Pseudocholinesterase deficiency can result in higher levels of intact succinylcholine
 molecules reaching receptors in the neuromuscular junction, causing the duration of
 paralytic effect to continue for as long as 8 hours.
- This condition is recognized clinically when paralysis of the respiratory and other skeletal
 muscles fails to spontaneously resolve after succinylcholine is administered as an
 adjunctive paralytic agent during anesthesia procedures.

Diagnosis:

• by plasma assays of pseudocholinesterase enzyme activity.

Management

- prolonged ventilation until the action of the drug wears off.
- Relatives of affected patients should be screened.

Prognosis

- exposed to succinylcholine →excellent when close monitoring and respiratory support measures
- exposed to cocaine, sudden cardiac death can occur.

Succinvl choline

- Depolarizing Skeletal muscle relaxants
- Also called suxamethonium
- Analogue of acetyl choline, acts on nicotinic Nm receptors
- · Only depolarizing skeletal muscle relaxant
- Fastest onset of action, Shortest duration of action
- can stimulate autonomic ganglia
- Side effect and contraindications (CI)
 - ⇒ Cause hyperkalemia in patients with nerve and muscular disorders so Cl in:
 - nerve disorders (Paraplegia, hemiplegia, GBS) and
 - muscular disorders(muscular dystrophy, Myasthenia, crush injury, burns, rhabdomyolysis)
 - ⇒ Increases all pressures so Cl in:

- glaucoma,
- head injury,
- increase BP.
- nausea and vomiting due to intragastric pressure.
- ⇒ Trigger malignant hyperthermia when used with halothane

Local spinal anesthetics

Hypotension and bradycardia following spinal anesthesia suggest neurogenic shock.

- Local spinal anesthetics, can interrupt the transmission of nerve impulses in spinal sympathetic pathways, causing a loss of sympathetic vascular tone that ultimately results in neurogenic shock.
- Neurogenic shock is a type of distributive shock characterized by:
 - ⇒ generalized vasodilation (causing diaphoresis and flushed skin).
 - ⇒ This vasodilation leads to decreased preload and subsequently reduced cardiac output, which results in **hypotension** and **bradycardia**.
 - ⇒ Consequently, cerebral perfusion is impaired, leading to a **loss of consciousness**.

Fentanyl

- Large, rapidly given doses of specific opioids such as fentanyl, sufentanil, remifentanil, and alfentanil are associated with systemic skeletal muscle rigidity.
 - Of most concern to the anesthesiologist is chest wall rigidity (which impairs mask and bag ventilation) and rigidity of the jaw muscles which can prevent the insertion of an advanced airway.

Ketamine

Ketamine is commonly used as a recreational drug.

adverse effects include:

- stimulation, euphoria, depersonalisation, floating feeling
- synaesthesia (a sensory stimulus in one modality is perceived as a sensation in another),
 eq: being able to 'smell sounds'
- delirium,
- vivid dreams
- hallucinations.

Topoisomerase inhibitors

Overview

- Topoisomerase I and II are enzymes that control the changes in DNA structure during the normal cell cycle.
- Topoisomerase inhibition leads to apoptosis and cell death.
- Used in:
 - ⇒ chemotherapy treatments.
 - ⇒ as antibacterial agents :Quinolones (including nalidixic acid and ciprofloxacin)

Topoisomerase I inhibitors

- Agent:
 - ⇒ Irinotecan: used mainly for Colorectal cancer
 - ⇒ Topotecan: used mainly for Ovarian cancer and Small-cell lung cancer

- Mechanism of action: Inhibition of topoisomerase I → ↓ DNA unwinding → ↓ DNA replication and DNA degradation (because of ssDNA breaks)
- Side effects: Myelosuppression and GI symptoms (e.g., diarrhea)

Topoisomerase II inhibitors

- Agent: Etoposide
- Indications: used for Solid tumors, Testicular cancer, Small-cell lung cancer, Leukemias, Lymphomas
- Mechanism of action: Inhibition of topoisomerase II → ↑ DNA degradation (dsDNA breaks) and ↓ DNA replication (cell cycle arrest in S and G2 phase)
- Side effects: Myelosuppression, Alopecia

By what mechanism does topoisomerase catalyse DNA replication?

- Helix torsion release
 - Topoisomerase releases torsion in the DNA helix during replication. It accomplishes this by cutting the DNA helix at specific points to allow it to unravel and then ligates the ends together again. This allows large proteins such as DNA polymerase to replicate DNA along the sequence.

Notes & Notes

For MRCP part 1 & 11

By

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Basic sciences Biochemistry & metabolism

Updated

Anion gap (AG)

Renal tubular acidosis causes a normal anion gap

- The anion gap allows for the differentiation of 2 groups of metabolic acidosis.
 - 1. Metabolic acidosis with a high AG is associated with the addition of endogenously or exogenously generated acids.
 - 2. Metabolic acidosis with a normal AG is associated with the loss of HCO3 or the failure to excrete H⁺ from the body.
- The anion gap is calculated by: (sodium + potassium) (bicarbonate + chloride)
- A normal anion gap is 8-14 mmol/L
- It is useful to consider in patients with a metabolic acidosis:
 - ⇒ Causes of a normal anion gap or hyperchloraemic metabolic acidosis
 - gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
 - renal tubular acidosis
- drugs: e.g. acetazolamide
- ammonium chloride injection
- Addison's disease
- ⇒ Causes of a raised anion gap metabolic acidosis
 - lactate: shock, hypoxia
 - ketones: diabetic ketoacidosis, alcohol
- urate: renal failure
- acid poisoning: salicylates. methanol

mnemonic of high anion gap acidosis:

DR. MAPLES: D-DKA; R-renal; M-methanol; A-alcoholic ketoacidosis; P-paraldehyde, phenformin; L-lactic (ie, CO, HCN); E-ethylene glycol; S-salicylates

Remember the mnemonic MUDPILES → high anion gap acidosis

M	Methanol
U	Uremia
D	Diabetic ketoacidosis
Р	Paraldehyde
1	Infection
L	Lactic acidosis
Ε	Ethylene glycol
S	Salicylates

Metabolic acidosis associated with bladder reconstruction (e.g. for carcinoma of the bladder).

- Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild.
- Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient.
- Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and treat metabolic acidosis with intravenous fluids and bicarbonate.

Metabolic alkalosis

Pathophysiology

- Metabolic alkalosis may be caused by a loss of hydrogen ions (H+) or a gain of bicarbonate (HCO3).
- It is due mainly to problems of the kidney or gastrointestinal tract
- The initial disturbance of metabolic alkalosis is an increased HCO₃⁻ concentration, followed by a compensatory response of increased Pco₂.
- All renal tubular defects result in metabolic alkalosis, except for Fanconi syndrome.

ABG picture

- pH : Elevated
- PCO2: Expected compensatory response: ↑
- HCO3: Elevated

Compensation mechanism

- Hypoventilation is an immediate compensatory response to metabolic alkalosis.
- ↑ Arterial and CSF pH (with ↑ HCO3-) → ↓ stimulation of the medullary chemoreceptors → ↓ respiratory rate and/or tidal volume (hypoventilation) → ↑ CO2 retention → ↑ PCO2

Causes

- Vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenos, nasogastric suction)
- Diuretics
- Liquorice, carbenoxolone
- Hypokalaemia
- Bulimia nervosa

Primary hyperaldosteronism

- ⇒ Liddle syndrome
- · Cushing's syndrome
- · Bartter's syndrome
- · Gitelman syndrome
- Congenital adrenal hyperplasia

Mechanism of metabolic alkalosis

- The main mechanisms of metabolic alkalosis in the setting of <u>vomiting</u> are increased H+ excretion in the distal tubule and increased bicarbonate reabsorption in the proximal tubule.
 - ⇒ ECF depletion (vomiting, diuretics) → Na⁺ and Cl- loss → activation of reninangiotensin II-aldosterone (RAA) system → ↑ aldosterone → reabsorption of Na⁺ in exchange for H+ in the distal convoluted tubule
- In hypokalaemia, K⁺ shift from cells to ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality

A patient with liver cirrhosis develops metabolic alkalosis. What is the most likely pathological mechanism? → Reduced urea synthesis

A patient in the intensive care unit following liver transplant surgery has a metabolic alkalosis.

What is the most likely cause?

- Diuretic-induced volume depletion
 - Cirrhosis → hypoalbuminaemia → low colloid osmotic pressure → Relative volume depletion → ↑aldosterone, (which is not adequately metabolised by an impaired liver).
 - Furosemide use in the post-operative period further exacerbates alkalosis driven by hyperaldosteronism.

Aetiology of metabolic alkalosis

Mechanism	Causes
Chloride-responsive metabolic alkalosis (urine chloride < 25 mEq/L)	 Gastrointestinal losses: due to vomiting, nasogastric suction, or diarrhea Renal losses: due to loop or thiazide diuretics Cystic fibrosis
Chloride-resistant metabolic alkalosis (urine chloride > 40 mEq/L)	 Severe magnesium deficiency Extreme hypercalcemia, hypokalemia High alkali load (e.g., due to antacid use, alkalization therapy) Loop or thiazide diuretics Other (less common causes) Associated with low or normal blood pressure Bartter syndrome Gitelman syndrome Associated with high blood pressure Hyperaldosteronism Cushing syndrome Liddle syndrome Liddle syndrome Licorice ingestion Ingestions or drugs (Laxative abuse, ampicillin, penicillin) Recovery from starvation Hypoalbuminemia

Prognosis

• when the pH is greater than $7.65 \rightarrow$ mortality rate is 80%

Treatment

- Chloride-responsive metabolic alkalosis
 - ⇒ Start isotonic saline to increase urinary bicarbonate excretion and correct extracellular volume loss
- Chloride-resistant metabolic alkalosis
 - ⇒ Consider bicarbonate excess as a potential cause and administer acetazolamide.
 - ⇒ Acetazolamide is a diuretic used to alkalinize the urine or treat metabolic alkalosis as it inhibits carbonic anhydrase.

Respiratory acidosis

Causes

Mechanism	Causes
Acute respiratory acidosis	 Acute lung disease (e.g., pneumonia , pulmonary edema) Acute exacerbation of chronic obstructive airway disease (e.g., COPD, asthma) CNS depression due to: Head trauma Postictal state Drug toxicity (e.g., from opiates, barbiturates, benzodiazepines) Central sleep apnea
Chronic respiratory acidosis	Airway obstruction (e.g., COPD, asthma) Respiratory muscle weakness, e.g., due to: Myasthenia gravis ALS Guillain-Barré syndrome Poliomyelitis Multiple sclerosis Severe hypokalemia

Features

Signs and symptoms of respiratory acidosis						
Central nervous system	Respiratory system	Cardiovascular system				
Cerebral vasodilation	Breathlessness	Flushing, bounding pulse				
Increased intracranial pressure	Cyanosis	Cor pulmonale				
Headache, confusion, agitation	Pulmonary hypertension	Systemic hypotension				
Hallucinations, transient psychosis		Arrhythmias				
Myoclonic jerks, flapping tremor, extensor plantars, depressed reflexes		Initially good cardiac output, then decreases				
Papilloedema, constricted pupils						
Seizures, coma						

Mechanism

Alveolar hypoventilation → CO2 retention

ABG picture

- wol : Hq
- PCO2: elevated
- HCO3: Expected compensatory response: ↑

Treatment

Consider noninvasive or invasive mechanical ventilation.

Respiratory alkalosis

Mechanism

↑ Respiratory rate and/or tidal volume → alveolar hyperventilation → CO2 washout

Causes

- Anxiety leading to hyperventilation (Hyperventilation will result in carbon dioxide being 'blown off', causing an alkalosis.) → high PH, low PCO2, normal PO2.
 - ⇒ not associated with hypoxia.
- · pulmonary embolism
- · Acute severe asthma
 - ⇒ associated with hypoxia and normal or rising CO₂
- Drugs (salicylates, progesterone)
 - ⇒ salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis.
 - Early stimulation of the respiratory centre leads to a respiratory alkalosis
 whilst later the <u>direct acid effects of salicylates</u> (combined with acute renal
 failure) may lead to an <u>acidosis</u>.
- · CNS disorders: stroke, subarachnoid haemorrhage, encephalitis
- High altitude
- Pregnancy
- Pain
- · Excessive mechanical ventilation.
- · Hepatic failure

ABG picture

- · pH : elevated
- PCO2: low
- HCO3: Expected compensatory response: ↓

Differential diagnosis of respiratory alkalosis with type 1 respiratory failure (low pO₂ and low pCO₂.):

- · Chronic venous thromboembolism (most likely).
- Pulmonary fibrosis (but basal crackles may be expected).

Calcium metabolism see endocrinology

Hypercalcaemia see endocrinology

Hypocalcaemia see endocrinology

Vitamin D see endocrinology

Hyperkalaemia

Definition

Serum potassium level > 5 mEq/L

Regulation

- Plasma potassium levels are regulated by a number of factors including:
 - ⇒ Aldosterone
 - ⇒ acid-base balance
 - ⇒ insulin levels.
- Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule.

Causes

- Potassium excess: due to altered K+ metabolism or intake
 - ⇒ **Reduced excretion:** acute and chronic kidney disease
 - ⇒ **Endocrine causes:** hypocortisolism, hypoaldosteronism
 - ⇒ Drugs: potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers, NSAIDs, and trimethoprim-sulfamethoxazole
 - ⇒ Type IV renal tubular acidosis
 - ⇒ Increased intake
 - High potassium diet, e.g., bananas, oranges, kiwi fruit, avocado, spinach, tomatoes
 - K+ containing IV fluids

Extracellular shift

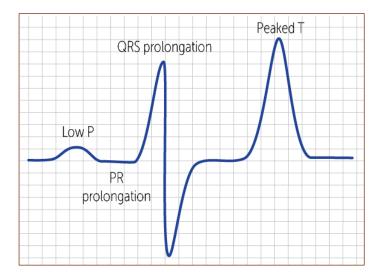
- ⇒ Acidosis → ↑ extracellular H+ → inhibition of the Na+/H+ antiporter → ↓ intracellular Na+ → ↓ sodium gradient inhibits the Na+/K+-ATPase → ↑ extracellular K+ concentration
 - Hyperkalemia → ↑ extracellular K+ concentration → ↑ potassium gradient stimulates the Na+/K+-ATPase → ↑ extracellular Na+ → ↑ sodium gradient stimulates the Na+/H+ antiporter → ↑ extracellular H+ → acidosis
 - Exceptions: In renal tubular acidosis and acetazolamide toxicity, findings include hypokalemia and metabolic acidosis.
- ⇒ Hyperosmolality
- ⇒ **Insulin deficiency** (manifests with hyperglycemia)
- ⇒ Drugs
 - Beta blockers
 - Succinylcholine: (esp. when given with preexisting burns and/or muscle trauma),
 - Digoxin: inhibits the Na+/K+-ATPase → ↑ extracellular K+ concentration
- Extracellular release
 - ⇒ Pathological cell lysis
 - Rhabdomyolysis
 - Tumor lysis syndrome
 - Hemolysis
 - ⇒ **High blood cell turnover:** e.g., thrombocytosis, erythrocytosis, leukocytosis
 - ⇒ **Pseudohyperkalaemia:** resulting from iatrogenic red blood cell lysis
 - Blood drawn from the side of IV infusion or a central line without previous flushing
 - Prolonged use of a tourniquet

- Fist clenching during blood withdrawal
- Delayed sample analysis

When K+ shifts out of the cell, it's a BAD LOSS! – Beta blockers, Acidosis, Digoxin, Lysis, hyperOsmolality, high Sugar, Succinylcholine

Features

- May be asymptomatic
- Nausea, vomiting, diarrhea
- Cardiac: Arrhythmias (e.g., atrioventricular block, ventricular fibrillation)
- $\bullet \quad \textbf{Neuromuscular:} \ \textbf{Muscle} \ \textbf{weakness}, \ \textbf{paralysis}, \ \textbf{paresthesia}, \ \downarrow \ \textbf{Deep tendon reflexes}$
 - ⇒ Weakness and fatigue are the most common complaints
- ECG changes
 - ⇒ **Early changes** (typically seen at a serum potassium level of 5.5-6.5 mEq/L)
 - tall, peaked T waves
 - shortened QT interval
 - ST-segment depression.
 - ⇒ At a serum potassium level of 6.5-8.0 mEq/L, in addition to peaked T waves:
 - Decreased or disappearing P wave
 - Prolonged PR interval
 - Widening of the QRS
 - Amplified R wave



Treatments

Immediate treatment principles include:

- 1. Providing calcium salts to reduce the risk of arrhythmia ('protect the heart');
- 2. Administering intravenous glucose and insulin ('shift potassium into cells');
- 3. Reducing intake and increasing output of potassium ('remove potassium from the body').

- Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors).
- Mild chronic hyperkalaemia (eg: 5.6 mmol/l) is well tolerated and not a cause for concern. If serum potassium rise to >6.0 mmol/l, standard practice would be to stop the ACEi and - if K >6.0 mmol/l were to persist - to advise a low potassium diet.
- Stabilisation of the cardiac membrane
 - ⇒ intravenous 10 ml 10% calcium gluconate (or calcium chloride)
 - ⇒ The effects of intravenous calcium occur within 1 to 3 minutes but last for only 30 to 60 minutes.
- Short-term shift in potassium from extracellular to intracellular fluid compartment
 - ⇒ Combined insulin/dextrose infusion:
 - ⇒ The most effective agent .
 - ⇒ In hyperglycaemic patients (serum glucose >15 mmol/L) insulin may be given without additional intravenous glucose.
 - ⇒ The dose: 10 units of soluble insulin
 - ⇒ Nebulised salbutamol
 - Less effective than iv insulin and glucose (not recommended as monotherapy)
 - Patients prescribed beta blockers may be 'resistant' to the hypokalaemic effects of salbutamol.
- Removal of potassium from the body
 - ⇒ Calcium resonium (orally or enema)
 - ⇒ Loop diuretics
 - ⇒ Dialysis

May 2020 exam: H/O muscle weakness and lethargy. K+ = 6.3 mmol/l. What is the most appropriate initial treatment to lower the serum potassium level?

→ Insulin/dextrose infusion

Pseudohyperkalaemia

High cell counts and high potassium: consider pseudohyperkalaemia

Causes

- Haemolysis during venepuncture
- Delay in the processing of the blood specimen
- Abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders or essential thrombocytosis)
- Familial causes

Management

- Re-check a fresh sample at the hospital
- Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium.

Hypokalaemia and acid-base balance

Hypokalaemia - U waves on ECG

Definition

• Serum potassium (K+) level < 3.5 mEq/L

Causes

Hypokalaemia with alkalosis

- Vomiting
- Diuretics

- · Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis

- Diarrhoea
- Renal tubular acidosis
- Acetazolamide
- · Partially treated diabetic ketoacidosis

Drug induced hypokalaemia

- Intracellular shifts of potassium with normal total body potassium, for example:
- theophylline

caffeine

β-agonists

⇒ insulin

Other causes

- · Loss of potassium stores, for example: chronic diuretic use
- Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the
 potassium level may be difficult until the magnesium deficiency has been corrected

In hyperthermia, as body temperature increases, what is <u>the earliest biochemical</u> abnormality?

- Hypokalaemia
 - As body temperature increases, such as occurs in hyperthermia due to heatstroke, the earliest abnormality is hypokalaemia.
 - This is thought to be due to increased K+ uptake by muscles as catecholamines stimulate the NA-K-ATPase transporter.
 - As the body temperature rises further, hyperkalaemia can develop with rhabdomyolysis and lactic acidosis.
 - The acid-base picture is of metabolic acidosis with compensatory respiratory alkalosis.

K+ acts like H+: Hypokalemia leads to alkalosis and vice versa

Hypomagnesemia can lead to refractory hypokalemia

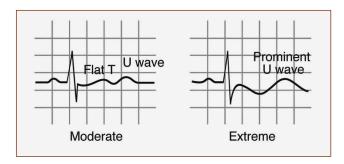
Features

- Cardiovascular : cardiac arrhythmias
- Neuromuscular:
 - o Muscle cramps and spasms
 - Muscle weakness

- Decreased deep tendon reflexes
- Gastrointestinal: Constipation

ECG findings in hypokalemia

- Mild to moderate hypokalemia
 - ⇒ T-wave flattening or inversion
 - ⇒ ST depression
 - ⇒ Prolonged PR interval
- Moderate to severe hypokalemia
 - ⇒ QT prolongation
 - ⇒ Presence of U waves



Treatment

- If K >2.5 with no symptoms or ECG changes → oral potassium
- If K <2.5 with symptoms or ECG changes → IV potassium
- In life-threatening cases → 1L IV 0.9% NaCL with 40 mmol/l KCl infused over four hours
 - ⇒ Cardiac monitoring.
 - ⇒ Potassium should be given in NaCl.
 - ⇒ Concentration should not exceed 40 mmol/l
 - ⇒ No more than 10-20 mmol/hour should be given.

In patients with hypokalemia, avoid solutions containing dextrose, which can increase insulin secretion and worsen hypokalemia.

Daily maintenance requirements (NICE guidelines):

- Water → 1500-2500 ml/ day (25-30 ml/kg/day)
- Potassium, Sodium and Chloride → 1 mmol/kg/day
 - **⇒** Sodium → 70 mmol
 - ⇒ potassium → (40-80 mmol/day) In the absence of kidney disease or hyperkalaemia (around 1 mmol/kg per day)

Estimation of total body potassium loss:

a drop in 1 mmol/L K⁺ of serum potassium in approximately equivalent to a 200 mmol K⁺ total body loss.

Hypernatraemia

Hypernatraemia associated with hypovolaemia occurs due to a free water deficit.

Common causes include reduced water intake (e.g. elderly), GI losses (e.g. vomiting and diarrhoea), skin losses (e.g. burns), and renal losses (e.g. osmotic diuresis)

Hypernatraemia associated with hypervolaemia can occur due to hypertonic saline, hypertonic sodium bicarbonate, excess salt in diet, or hyperaldosteronism

Causes

- Insufficient water
- free water loss:
 - ⇒ renal (diabetes insipidus, diuretics, osmotic diuresis as with hyperglycaemia),
 - ⇒ GI (diarrhoea, vomiting),
 - ⇒ skin (sweating, burns)
- Salt overload e.g. acute salt poisoning (hypertonic saline, hypertonic sodium bicarbonate), hyperaldosteronism

Treatment

- Treatment is aimed at the underlying cause.
- Hypernatraemia should be corrected with great caution.
- Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death.
- acute hypernatraemia can be corrected quickly but if chronic (>24hours) then it should be corrected at <0.5mmol/L/hr.
- Fluid resuscitation should involve oral water, 0.45% saline or 5% dextrose IV.

Hyponatraemia (serum sodium less than 135 mEg/L)

Mechanisms of causes

- Water excess
- 2. Sodium depletion.
- 3. Pseudohyponatraemia:
 - ⇒ hyperlipidaemia (increase in serum volume)
 - ⇒ hyperproteinemia (e.g: myeloma)
 - ⇒ taking blood from a drip arm.

Cause of hyponatraemia

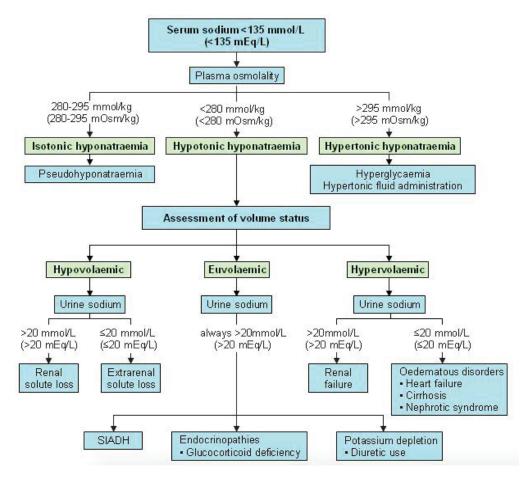
Urinary sodium > 20 mmol/l		Urinary soc	lium < 20 mmol/l
Sodium depletion, renal loss (patient often hypovolaemic)	Patient often euvolaemic	Sodium depletion, extra-renal loss (hypovolaemic)	Water excess (patient often hypervolaemic and oedematous)
diuretics Addison's diuretic stage of renal failure	SIADH (urine osmolality > 500 mmol/kg) hypothyroidism	diarrhoea, vomiting, sweating burns, adenoma of rectum	secondary hyperaldosteronism: heart failure, cirrhosis reduced GFR: renal failure IV dextrose, psychogenic polydipsia

Features

- Fatigue
- · Muscle weakness
- · Gait disturbance
- Falls
- Disorientation
- · Cerebral oedema
- Seizures

Investigations

- Urinary sodium and osmolarity levels aid making a diagnosis.
 - □ urinary sodium
 - Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal.
 - may be misleading in the presence of renal impairment or diuretic therapy.



Management

- It is important with hyponatraemia to ascertain volume status as this will determine management.
- The management of each is as follows:
 - ⇒ Hypovolaemic hyponatraemia
 - Diagnosis may supported by an elevated urea suggesting dehydration.
 - rehydration with sodium chloride 0.9% or a balanced crystalloid (Hartmann's)
 - avoid rapid correction of sodium in order to reduce the risk of osmotic complications such as central pontine myelinolysis
 - The rate of correction of hyponatremia should not exceed <u>eight</u> mEq/L per day.

⇒ Euvolaemic hyponatraemia

- check urine and serum osmolality. Does the patient meet the criteria for SIADH?
- treat the underlying cause where possible in SIADH
- fluid restriction (500-750mls/day)
- monitor fluid balance and perform daily weights
- consider demeclocycline or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone.

⇒ Hypervolaemic hyponatraemia

- fluid and salt restriction
- consider diuretics
- treat the underlying cause (e.g. cardiac failure)

Hyponatraemia: correction

Acute hyponatraemia is that which occurs within a duration of 48 hours.

Acute hyponatraemia

- predisposing factors to acute hyponatraemia:
 - ⇒ Over consumption of fluids,
 - ⇒ prolonged race duration and inadequate training
- Pathophysiology
 - ⇒ When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result patients may die from brain herniation.
- Treatment
 - ⇒ The correct treatment to give is hypertonic saline.
 - ⇒ Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment.
 - ⇒ A small, quick increase in the serum sodium is required in order to decrease intracranial pressure. Hypertonic saline (3%) boluses are the most appropriate treatment to improve neurological status in such patients.

Hyponatremia in patients with advanced cirrhosis

- Mechanism
 - ⇒ systemic vasodilation, (The most important factor) which leads to activation of endogenous vasoconstrictors including antidiuretic hormone (ADH); ADH promotes the water retention that is responsible for the fall in serum sodium.
- Tolvaptan (Vasopressin receptor antagonists) should not be used in patients with cirrhosis, because of its known potential for hepatotoxicity.

Central pontine demyelinolysis

Central pontine myelinolysis (CPM):

- · Due to rapid correction of hyponatraemia
- the classical presentation is spastic quadriparesis, pseudobulbar palsy, and emotional lability (pseudobulbar affect) (<u>locked in</u> syndrome.)
- **Definition:** damage to the myelin sheath of the white matter in the CNS caused by a sudden rise in serum osmolality (rapid correction of chronic hyponatremia)
- Affects the central region of the pons
- Pathophysiology: rapid sodium correction → Sudden rises in plasma osmolarity → fluid shift from the cerebral intracellular space to the extravascular space (<u>loss of water from the intracellular compartment</u>) → cerebral shrinking and demyelination → end result is central pontine myelinolysis (CPM).
- Features
 - ⇒ Symptoms first develop several days after the correction of hyponatremia.
 - ⇒ Central pontine myelinolysis
 - Altered level of consciousness, including coma
 - Locked-in syndrome
 - Impaired cranial nerve function: dysarthria, dysphagia, and diplopia
 - Worsening quadriparesis
- **Diagnosis**: MRI brain
- Treatment: supportive care
- **Prevention:** Avoid hypernatremia
 - ➡ Many authorities recommend that increases in serum sodium of <12 mmol/24 hours are likely to be safe for the majority of patients.</p>
 - ⇔ Certain patients with hypokalaemia, liver disease, poor nutritional state or burns are at higher risk of demyelination and should have a rate of sodium correction of <8 mmol/24 hours.
 </p>

"Saline depletion, for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's."

Osmolar gap

- Osmolar gap is the difference between the calculated osmolarity and the measured osmolality.
- The normal value is 10-15 but may be increased in the presence of unmeasured 'abnormal' osmotically active ions in the plasma.
- An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute that may be present in significant amounts.
- Ethanol, ethylene glycol (anti-freeze), acetone and methanol are solutes that will cause elevation of the osmolar gap in this way.
- Calculated osmolarity = 2 (Na + K) + Glucose + Urea (all in mmol/L).
- Normal serum osmolarity is 285-295 mOsm/L.
- Osmolality is measured in the laboratory using an osmometer.

Hypomagnesaemia

Definition

Low magnesium below 0.7 mmol/L .

Overview

- Normal plasma magnesium (0.7-0.9 mmol)
- The thick ascending limb (TAL) of the loop of Henle is the major site of reabsorption (60-70%) (unlike most ions, those reabsorbed in the proximal convoluted tubule)
- In the TAL, magnesium is passively reabsorbed. In the distal convoluted tubule, magnesium is reabsorbed via an active, transcellular TRPM6 channel.

Uses for magnesium include:

- polymorphic ventricular tachycardia (torsade de pointes),
- acute asthma
- prevention/treatment of seizures in pre-eclampsia.
- Magnesium salts can be given as laxatives

Causes of low magnesium

- Inadequate intake:
 - ⇒ Malnutrition, and
 - Alcohol dependence. Hypomagnesemia is the most common electrolyte abnormality observed in alcoholic patients
 - ⇒ Total parenteral nutrition

Malabsorption:

- ⇒ Inflammatory bowel disease
- ⇒ Long term PPI therapy
- ⇒ Gluten enteropathy
- ⇒ Intestinal bypass, and
- ⇒ Radiation enteritis.

· Renal tubular disease:

- ⇒ Hyperaldosteronism
- ⇒ Hyperparathyroidism
- ⇒ Obstructive uropathy
- ⇒ Potassium depletion, and
- ⇒ Drugs (including diuretics, amphotericin, cisplatin, ciclosporin, amikacin, gentamicin, laxatives, and tacrolimus).

Intracellular shift:

- ⇒ Post myocardial infarction
- ⇒ Post parathyroidectomy
- ⇒ Recovery from diabetic ketoacidosis (K+ and PO₄- also enter cells)
- ⇒ Refeeding syndrome (PO₄- also enters cells),
- ⇒ Acute pancreatitis.

Drugs:

- diuretics
- cyclosporine
- ⇒ cardiac glycosides
- ⇒ Colorectal cancer treatment with cetuximab/panitumumab (EGF receptor inhibitors) → ↓ TRPM6 → hypomagnesemia.
- → Omeprazole → hypomagnesaemia → hypoparathyroidism → hypocalcaemia.

- Diarrhoea
- · Metabolic acidosis
 - □ Chronic metabolic acidosis → \pirenal TRPM6 expression in the DCT → \pi Mg reabsorption → \pi serum Mg.
- Hypercalcaemia
 - ⇒ Hypercalcemia → activation of calcium-sensing receptor (CaSR) → ↓ Mg reabsorption
- Hypokalaemia, hypocalcaemia
- Genetic diseases

Features

- General
 - ⇒ lack of appetite.
 - ⇒ Lethargy
 - ⇒ fatigue
- neuromuscular hyper-excitability
 - muscle weakness including fasciculations
 - ⇒ changes in personality
 - **⇒** paraesthesia
 - ⇒ tetany
 - ⇒ seizures

- cardiac
- arrhythmias
- ECG features similar to those of hypokalaemia
- The ECG change most typically associated with hypomagnesaemia is QT prolongation.
- · exacerbates digoxin toxicity
- decreased PTH secretion → hypocalcaemia
- Hypokalemia (in 40-60%)

Associations with hypomagnesemia

- Hypoparathyroidism
 - ⇒ ↓ Mg →↓ magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP) → ↓PTH → hypoparathyroidism
- DM (↓ Mg →↓ insulin sensitivity and secretion)
- Cardiac: CAD, Hypertension (Mg plays a role in BP regulation), cardiac arrhythmia (prolongation of the QT interval, Torsade de pointes)

Investigation

- blood magnesium levels can guide but do not accurately reflect total body magnesium status. Attempts to find a marker of cellular magnesium status include measuring erythrocyte or monocyte Mg but these are not generally available.
- Urine Mg excretion is a useful guide. When there is inadequate intake or malabsorption, the kidneys would normally conserve Mg, giving urine Mg concentrations <7 mmol/24 hours. The reference range is around 2-7 mmol/24 hours.

Treatment

- <0.4 mmol/l
 - ⇒ intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours
- >0.4 mmol/l
 - ⇒ oral magnesium salts (10-20 mmol orally per day)
 - ⇒ diarrhoea can occur with oral magnesium salts

Hypermagnesaemia

Overview

 Hypermagnesaemia is much less common than hypomagnesaemia and is often iatrogenic in cause.

Causes of hypermagnesaemia

- latrogenic:
 - ⇒ Treatment with magnesium sulphate to prevent/treat seizures in patients with eclampsia or pre-eclampsia
 - ⇒ Treatment with Mg containing antacids
 - ⇒ Use of citrate-glucuronic acid solutions to dissolve renal calculi either through bladder irrigation or via a nephrostomy tube
 - ⇒ Over-zealous IV treatment of hypomagnesaemia
 - ⇒ Chronic use of Mg-containing enemas.
- · Other causes:
 - ⇒ Acute or chronic renal failure
 - release of Mg from tissues,
 - Mg in dialysate,
 - Mg in phosphate binding drugs
 - ⇒ Familial hypocalciuric hypercalcaemia.

Lithium can cause hypermagnesaemia

Features

- · Mild hypermagnesemia often asymptomatic
- Nausea, Lethargy
- · Reduced deep tendon reflexes
- Blurry vision
- Cardiac: Vasodilatation, Hypotension, Bradycardia
- ECG changes: ↑ PR interval, ↑ QRS duration, ↑ QT interval
- Blurry vision
- Hypocalcemia
- Severe hypermagnesemia
 - ⇒ Muscle paralysis (flaccid quadriplegia)
 - ⇒ Bradycardia, Cardiac arrest
 - ⇒ Respiratory failure

Treatment

- If mild/moderate and iatrogenic, often it is enough to identify and stop the cause.
- In an emergency, dialysis or administration of IV calcium glucuronate (10 ml of 10%) will reduce the effects of hypermagnesaemia.

Hypophosphataemia

Definition

• serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L).

Causes

Causes	Consequences
 alcohol excess acute liver failure diabetic ketoacidosis refeeding syndrome primary hyperparathyroidism osteomalacia Hyperventilation 	 red blood cell haemolysis white blood cell and platelet dysfunction muscle weakness and rhabdomyolysis central nervous system dysfunction

Mechanisms

- The three major mechanisms of hypophosphataemia are:
 - 1. Redistribution of extracellular phosphate into cells
 - hyperventilation → respiratory alkalosis → activating phosphofructokinase
 → moves phosphate into cells → stimulates intracellular glycolysis.
 - Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced.
 - Any cause of hyperventilation (eg, sepsis, anxiety, pain, heatstroke, alcohol withdrawal, diabetic ketoacidosis [DKA], hepatic encephalopathy, salicylate toxicity, neuroleptic malignant syndrome [NMS]) can precipitate hypophosphatemia.
 - 2. Decreased intestinal absorption,
 - chronic diarrhea,
 - malabsorption syndromes,
 - severe vomiting,
 - nasogastric (NG) tube suctioning.
 - 3. Depletion due to increased urinary loss.
 - the most common cause of hypophosphatemia
 - primary and secondary hyperparathyroidism.
 - Osmotic diuresis, such as seen in hyperosmolar hyperglycemic syndrome (HHS)
 - Fanconi syndrome (proximal tubule dysfunction)
 - X linked hypophosphataemic rickets
 - Oncogenic hypophosphataemic osteomalacia

MRCPUK- part-1-Sep 2017: what is the mechanism of Hypophosphataemia during treatment of DKA?

→ Shift from extracellular to intracellular space

MRCPUK-part-1-Sep 2017: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission ?

- → Shift from extracellular to intracellular space
 - The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells.
 - Two factors may contribute to this shift:
 - I.V therapy with dextrose-containing solutions or refeeding → ↑Glucose
 → ↑ insulin release → ↑ phosphate uptake by the cells
 - alcohol withdrawal → hyperventilation →acute respiratory alkalosis
 →intracellular alkalosis → stimulates intracellular phosphofructokinase
 →↑ glycolysis → movement of phosphate into cells

Hyperphosphataemia

Overview

- The healthy adult usually ingests about 8400 mg per week of phosphate through their diet
- Absorption occurs mainly in the jejunum
- Renal reabsorption: the majority (70%) of filtered phosphate is reabsorbed by type 2a sodium phosphate cotransporters located on the apical membrane of the renal proximal tubule.
- The normal adult range for phosphorus is 2.5-4.5 mg/dL (0.81-1.45 mmol/L).
- Renal excretion: About 5400 mg of phosphate is excreted per week through the kidneys.

Causes

- · Usually iatrogenic
- __calcium + ↑ phosphate levels seen in (decreased phosphate excretion)
 - ⇒ renal failure
 - ⇒ hypoparathyroidism, and pseudohypoparathyroidism
- †calcium + †phosphate seen in
 - ⇒ vitamin D intoxication (↓PTH + ↑ vitamin D)
 - ⇒ milk-alkali syndrome (⊥PTH + ⊥vitamin D)
- Disorder that shifts intracellular phosphate to extracellular space
 - □ Tumor lysis
 - ⇒ Rhabdomyolysis
- **Increased phosphate intake** (e.g., phosphate-containing enemas)
 - ⇒ Laxative (Phospho-soda) abuse
 - ⇒ Foods that are characteristically rich in phosphate include: dairy products, (Cheddar cheese), fibre rich foods, chocolate, and processed meats.

Features

- Often asymptomatic
- High PO43- levels cause the formation of an insoluble compound with calcium, which can lead to:
 - ⇒ Hypocalcemia → hypocalcemic symptoms (muscle cramps, tetany, and perioral numbness or tingling).
 - ⇒ Nephrolithiasis
 - ⇒ Calcifications in the skin

Management

- Treat the underlying cause.
- Discontinue phosphate intake (dietary or medication).
- Give phosphate binders (e.g., aluminium hydroxide, calcium carbonate).
- Consider dialysis (especially in severe cases of hyperphosphatemia in patients with renal failure).

Collagen Types

Types of collagen		
	Tissue distribution	Related conditions
Type I collagen (90% of body collagen)	Bone (produced by osteoblasts), skin, tendons, ligaments, fascia, dentin, cornea, internal organs, scar tissue (late stages of wound healing)	Osteogenesis imperfecta type I: decreased production
Type II collagen	Cartilage (including hyaline), vitreous humor of the eye, intervertebral discs (nucleus pulposus)	Achondrogenesis (type II)
Type III collagen (reticulin)	Reticular fibers in skin, blood vessels, granulation tissue, uterus, scar tissue (early stages of wound healing), fetal tissue in early embryos and throughout embryogenesis	Ehlers-Danlos syndrome (vascular type): decreased production
Type IV collagen	Basement membranes, lens	Alport syndrome: decreased production Goodpasture syndrome: autoantibodies target type IV collagen
Type V collagen	Bone, skin, fetal tissue, placenta	Ehlers-Danlos syndrome (classic type)

Vitamin B3 (Niacin) deficiency

Causes

- Malnutrition
- Heavy drinking (more common in alcoholics)
- Conditions associated with tryptophan deficiency
 - ⇒ Hartnup disease: decreased renal and intestinal tryptophan absorption
 - ⇒ Carcinoid syndrome (if metabolically active): increased tryptophan metabolism
- Vitamin B6 deficiency (e.g., due to treatment with isoniazid): decreased niacin synthesis from tryptophan.

 Chronic consumption of grains that have not been processed by nixtamalization (common cause in developing countries)

Features

- Atrophic glossitis
 - ⇒ the tongue is pink or red
 - ⇒ appears glossy and smooth due to the atrophy of papillae.
 - ⇒ can be painful.
- Pellagra (caused by severe deficiency)
 - ⇒ Characteristic dermatitis
 - Circular broad collar rash on the neck (Casal necklace); affects dermatomes
 C3 and C4
 - Hyperpigmented skin lesions in sun-exposed areas (especially on the limbs)
 - ⇒ Diarrhea and vomiting
 - ⇒ Neurologic symptoms (e.g, dementia, hallucinations, anxiety, insomnia, encephalopathy)

Pellagra

- The classical features are the 3 D's Dermatitis, Diarrhoea and Dementia.
- Caused by nicotinic acid (niacin) deficiency.

itamin C (ascorbic acid) (scurvy)

- Vitamin C is a water soluble vitamin.
- Dehydroascorbic acid, the oxidative product of ascorbic acid metabolism, passively penetrates cellular membranes and is the preferred form for erythrocytes and leukocytes.

Functions

- Antioxidant (Ascorbic acid provides electrons needed to reduce molecular oxygen. These anti-oxidant capabilities also stabilize vitamin E and folic acid.)
- It is a cofactor for reduction of folate to dihydro-and-tetrahydrofolate.
 - ⇒ Therefore macrocytic anaemia in scurvy may occur due to two reasons:
 - oxidative hemolysis and
 - folate metabolism defects.
- collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen
 - ⇒ Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing
- · facilitates iron absorption
- cofactor for norepinephrine synthesis
- cofactor for reduction of folate to dihydro-and-tetrahydrofolate.

Causes

- occurs in people with poor dietary intake, who eat little or no fruit and vegetables, commonly alcoholics and elderly people existing on a 'tea and toast' diet.
- Pregnancy, lactation and thyrotoxicosis increase ascorbic acid requirements and may precipitated scurvy.

Features vitamin C deficiency

- · gingivitis, loose teeth
- poor wound healing

- · bleeding from gums, haematuria, epistaxis
- general malaise
- anaemia
 - macrocytic anaemia in scurvy may occur due to two reasons: oxidative hemolysis and folate metabolism defects.
 - ⇒ normochromic, normocytic anaemia reflects bleeding into tissues

Continued deficiency leads to:

Anaemia Myalgia Bone pain Bruising Petechial and perifollicular haemorrhages Corkscrew hairs Mood changes	Fragility scleral icterus (late, probably secondary to haemolysis), and pale conjunctiva. Fractures, dislocations and tenderness of bones are common in children. Bleeding into muscles and joints may be seen
---	--

Late stages can lead to:

Late Stages carriedu to:	
Generalised oedemaSevere jaundiceHaemolysisHaemorrhage	NeuropathyConvulsions, andDeath.

The classical skin manifestations of scurvy are:

- · perifollicular hyperkeratotic papules
- · perifollicular haemorrhages
- · purpura, and
- ecchymoses.

Treatment

- vitamin C supplementation,
- · recovery is usually complete within three months.

Vitamin B12 deficiency

Overview

- Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system.
- It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum.
- A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.
 - ⇒ Approximately 1 percent of a large oral dose of vitamin B₁₂ is absorbed by this second mechanism. This pathway is important in relation to oral replacement.
- Once absorbed, vitamin B₁₂ binds to **transcobalamin II** and is transported throughout the body.
- Exhaustion of vitamin B12 stores usually occurs after 12 to 15 years of absolute vitamin B12 deficiency.

Causes

- Malabsorption
 - ⇒ ↓ Intrinsic factor (IF)
 - · Atrophic gastritis due to
 - Autoimmune atrophic gastritis: most common cause of vitamin B12 deficiency

- H. pylori infection
- Gastrectomy
- ⇒ Reduced uptake of IF-vitamin B12 complex in terminal ileum due to:
 - Alcohol use disorder
 - Crohn disease, celiac disease
 - Pancreatic insufficiency
 - Surgical resection of the ileum
 - Diphyllobothrium latum (tapeworm) infection
 - · Bacterial overgrowth
 - Enteritis
 - Achlorhydria
- Malnutrition
 - ⇒ Strict vegan diets: occurs only after years of a strict diet that excludes all animal products (unlike folate deficiency, which occurs within a few months of insufficient intake)
- Increased demand: e.g., during pregnancy, breastfeeding, fish tapeworm (Diphyllobothrium latum) infection
- Metformin (Chronic metformin use results in vitamin B12 deficiency in 30% of patients)

Features

- Macrocytic anaemia
- · Sore tongue and mouth
- · Neurological symptoms:
 - ⇒ Peripheral neuropathy
 - ⇒ Subacute combined degeneration of spinal cord
 - ⇒ The neurological symptoms can occur without anemia
- Autonomic dysfunction: impotence and incontinence
- Psychiatric disorders symptoms: including impaired memory, irritability, depression, dementia and, rarely, psychosis
- · Cardiovascular effect:
 - ⇒ Similar to folic acid deficiency, vitamin B₁₂ deficiency produces hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease.
 - ⇒ Serum high concentrations of homocysteine and low levels of folic acid and vitamin B₁₂ are significantly correlated with the categories of coronary artery diseases

Investigations

- Serum cobalamin levels are the initial test
 - ⇒ A normal serum cobalamin level does not exclude cobalamin deficiency.
- Diagnosis of vitamin B₁₂ deficiency is typically based on measurement of serum vitamin B₁₂ levels; however, about 50 percent of patients with subclinical disease have normal B₁₂ levels.
- A more sensitive method of screening for vitamin B₁₂ deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B₁₂deficiency.
 - ⇔ elevated methylmalonic acid level is more specific for vitamin B₁₂ deficiency than an elevated homocysteine level.
 - ⇒ Vitamin B₁₂ or folic acid deficiency can cause the homocysteine level to rise, so folic acid levels also should be checked in patients with isolated hyperhomocysteinemia.
 - \Rightarrow two enzymatic reactions are known to be dependent on vitamin B₁₂.

- methylmalonic acid is converted to succinyl-CoA using vitamin B₁₂ as a cofactor. Vitamin B₁₂ deficiency, therefore, can lead to increased levels of serum methylmalonic acid.
- 2. homocysteine is converted to methionine by using vitamin B₁₂ and folic acid as cofactors. In this reaction, a deficiency of vitamin B₁₂ or folic acid may lead to **increased homocysteine levels**.

Management

- if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
 - ⇒ oral vitamin B₁₂ has been shown to have an efficacy equal to that of injections in the treatment of pernicious anemia and other B₁₂ deficiency states.
 - Although the daily requirement of vitamin B₁₂ is approximately 2 mcg, the initial oral replacement dosage consists of a single daily dose of 1,000 to 2,000 mcg. This high dose is required because of the variable absorption of oral vitamin B₁₂ in doses of 500 mcg or less.
- if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord
 - ⇒ Large amounts of folic acid can mask the damaging effects of vitamin B12 deficiency by correcting the megaloblastic anemia caused by vitamin B12 deficiency without correcting the neurological damage that also occurs

Sep 2017 part 1: Which structure in the body are able to synthesize vitamin B12?

gut bacteria

- It is synthesized by gut bacteria in humans, but humans cannot absorb the B₁₂ made in their guts, as it is made in the colon which is too far from the small intestine, where absorption of B₁₂ occurs.
- Therefore diet is the only source of vit B12.

Vitamin B1 (Thiamine) deficiency

Overview

- the biologically active form of this vitamin is **thiamine pyrophosphate** (TPP)
- the most important biochemical reactions requiring the availability of thiamine includes glycolysis and tricarboxylic acid (TCA) cycle.
- There are three enzymes that require the presence of thiamine pyrophosphate as a cofactor:
 - 1. a-ketoglutarate dehydrogenase
 - 2. branched chain amino acid dehydrogenase
 - 3. pyruvate dehydrogenase

Causes

- · Heavy alcohol drinking
- Malnutrition, starvation
- Malabsorption
- Malignancy

Pathophysiology

- Thiamine deficiency → impaired glucose breakdown → ATP depletion → tissue damage that primarily affects highly aerobic tissues (e.g., brain, heart)
- High-dose glucose infusions lead to increased ATP depletion, which can trigger Wernicke encephalopathy.
 - In malnourished individuals and chronic alcohol users/heavy drinkers, thiamine should be administered before glucose infusions.

Features

- Beriberi: inadequate thiamine uptake due to malnutrition, heavy drinking, or increased demand (e.g., hyperthyroidism, pregnancy)
 - ⇒ Dry beriberi
 - Symmetrical peripheral neuropathy (sensory and motor)
 - Progressive muscle wasting
 - Paralysis
 - Confusion
 - ⇒ Wet beriberi
 - Oedema
 - High-output cardiac failure (dilated cardiomyopathy)
- Wernicke encephalopathy
 - ⇒ The triad of: Encephalopathy, Ataxia and Oculomotor dysfunction (usually nystagmus)
- Korsakoff's psychosis
 - ⇒ characterised by both anterograde and retrograde amnesia with confabulation

What happens if you do not give the thiamine first before starting an intravenous glucose infusion?

- ATP failing to be adequately generated
- The inability of pyruvate to enter the TCA cycle → accumulate of pyruvate → pyruvate converted to lactate in order to be able to maintain glycolysis → acidosis.
- Inability of the pentose phosphate pathway to protect the cell from reactive oxygen species that damage cellular structures, results in either cell death or activation of apoptosis.

Vitamin function as a co-factors:

- Biotin for carboxylase reactions.
- Thiamine for dehydrogenase reactions
- ⇒ B9 (folate) for transferases.
- Vit C for hydroxylases.

Vitamin E deficiency

Active form: tocopherol

Function

Lipid-soluble antioxidant in the glutathione peroxidase pathway → removes the free
radical intermediates → protects cell membranes from oxidation by reacting with lipid
radicals produced in the lipid peroxidation chain reaction.

Therapeutic uses → Nonalcoholic steatohepatitis

Features

- · Neurologic dysfunction
 - ⇒ Demyelination of the posterior column and spinocerebellar tract → ↓ proprioception and vibration sensation; ataxia
 - ⇒ Neurologic symptoms are similar to vitamin B12 deficiency, except that vitamin E deficiency does not lead to hypersegmented neutrophils, megaloblastic anemia, and increased methylmalonic acid levels.
- Hemolytic anemia; increased fragility of erythrocytes and membrane breakdown
- Acanthocytosis
- Muscle weakness

Hypervitaminosis E

 interfere with vitamin K metabolism → vitamin K deficiency → increased tendency to bleed.

Vitamin K Deficiency

Sources of vitamin K

- Leafy green vegetables (vitamin K1)
- · Synthesized in small amounts by intestinal bacteria

Functions

- Cofactor for γ-carboxylation of glutamate residues on vitamin-K-dependent proteins involved in:
 - Coagulation: maturation of factors II (prothrombin), VII, IX, and X, protein C, protein S
 - ⇒ Bone formation: osteocalcin (bone Gla protein), matrix Gla protein

Causes

- Liver failure
- Fat malabsorption
- Prolonged broad-spectrum antibiotic therapy
- Vitamin K antagonists (e.g., warfarin)

Features

- Hemorrhage (e.g., petechiae, ecchymoses)
- Vitamin K deficiency bleeding (VKDB)
 - ⇒ ↑ PT and aPTT, normal bleeding time
 - ⇒ Postnatal prophylaxis: vitamin K injection at birth

Vitamin A deficiency

Over view of vitamin A

- Active forms: Retinal and Retinoic acid
- Sources
 - ⇒ Plant sources; yellow and leafy vegetables
 - ⇒ Animal sources: in storage form; liver

Causes

• Disorders associated with fat malabsorption: inflammatory bowel disease (e.g., Crohn disease), celiac disease, cystic fibrosis, pancreatic insufficiency

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Features

- · Ocular manifestations
 - ⇒ Night blindness (nyctalopia)
 - ⇒ Xerophthalmia
 - ⇒ Keratomalacia
 - ⇒ Bitot spots: gray, triangular, dry patches on the bulbar conjunctiva, covered by a layer with a foamy appearance
 - Typical sign of vitamin A deficiency
 - Caused by squamous cell metaplasia and keratinization of the conjunctiva
- Keratinizing squamous metaplasia of the bladder (pearl-like plaques on cystoscopy)
- Xerosis cutis (dry skin)
- Immunosuppression

Vitamin A toxicity

- **⊃** Causes: increased intake via supplements or drugs
- → Acute toxicity: Nausea, vomiting, Vertigo, Blurred vision
- **○** Chronic toxicity:
 - Alopecia, Dry skin, scaling
 - Arthralgias
 - Hepatosplenomegaly, hepatic toxicity
 - Pseudotumor cerebri

Which substances in vitamin A is most likely to be maximally involved in correcting the visual disturbance?

- Retinaldehyde
 - Retinaldehyde is derived from the oxidation of retinol

What would you give the patient who taking long term steroids to help his wound heal faster?

- Vitamin A
 - Vitamin A is believed to counteract the effect of steroids on slowing wound healing by stimulating TGF-beta and IGF-I, as well as collagen production. However, high levels (which can accumulate because vitamin A is fat soluble) can also be toxic and inhibit collagen synthesis, such as in the skin.

Vitamin deficiency

The table below summarises vitamin deficiency states

Vitamin	Chemical name	Deficiency state
А	Retinoids	Night-blindness (nyctalopia). dry skin.
B1	Thiamine	Beriberi polyneuropathy, Wernicke-Korsakoff syndrome heart failure (dilated cardiomyopath)
B2	(riboflavin)	Angular stomatitis, cheilosis, corneal vascularization
В3	Niacin	Pellagra
B6	Pyridoxine	Anaemia, irritability, seizures
B7	Biotin	Dermatitis, seborrhoea
В9	Folic acid	Megaloblastic anaemia, deficiency during pregnancy - neural tube defects
B12	Cyanocobalamin	Megaloblastic anaemia, peripheral neuropathy
С	Ascorbic acid	Scurvy
D	Ergocalciferol, cholecalciferol	Rickets, osteomalacia
Е	Tocopherol, tocotrienol	↑ fragility of RBCs. Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy
К	Naphthoquinone	Haemorrhagic disease of the newborn, bleeding diathesis
Selenium	Selenium	Keshan disease (cardiomyopathy).

Zinc deficiency

Features

- perioral dermatitis: red, crusted lesions
- (rough and dry skin)
- acrodermatitis
- alopecia
- short stature (dwarfism)
- hypogonadism
- hepatosplenomegaly
- geophagia (ingesting clay/soil)
- cognitive impairment

Treatment

- Zn supplementation has been shown to improve neuropsychological function in Chinese children.
- Zn deficiency is associated with adverse pregnancy outcomes.

Pyruvate kinase

- Pyruvate kinase is the rate-limiting step in glycolysis and gluconeogenesis
- It catalyses the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding a
 molecule of pyruvate and a molecule of ATP
- Deficient pyruvate kinase activity may result in the development of hereditary haemolytic anaemias

Which biochemical processes is likely to contribute most to energy creation in long distance running?

→ Fatty acid oxidation

Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic sciences Immunology

Updated 2022

Human leukocyte antigen (HLA)

Overview

- The human leukocyte antigen (HLA) is a gene complex that encodes the major histocompatibility complex (MHC) proteins.
- MHC proteins play a vital role in initiating immune responses as they present antigen fragments to T cells and bind T-cell receptors.
- Found on chromosome 6
- 2 classes:
 - ⇒ Class I → HLA A . B. C
 - expressed on all cells, except erythrocytes and trophoblasts
 - interact with CD8+
 - ⇒ class II → HLA DP, DQ, DR
 - expressed on B cells, dendritic cells, and monocytes
 - most important in transplant → (DR)

MHC I-associated loci (HLA-A/-B/-C) only have 1 letter after the hyphen, while MHC II-associated loci (HLA- DR/- DP/- DQ) have 2 letters.

MRCP- part-1-2018: Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection?

- **⇒** HLA-C
 - Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection; specifically.
 - HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant.

HLA associations

• The most important HLA associations are listed below:

HLA type	Associated diseases	
HLA-A3	Hemochromatosis	
HLA-B5	Behcet's disease HLA B51 is a split of B5	
HLA- B47	21-hydroxylase deficiency	
HLA-CW6	⇒ Psoriasis	
HLA-DR3 + DR4 combined	⇒ Diabetes mellitus type 1(but more with HLA-DR4)	
HLA- DR7	steroid-responsive nephrotic syndrome	
HLA- DR2	 Narcolepsy Goodpasture's hay fever, systemic lupus erythematosus, multiple sclerosis. 	
HLA- DR4	 ⇒ Felty's syndrome (90%) → most common ⇒ Rheumatoid arthritis (70%) ⇒ Diabetes mellitus type 1 (> DR3) ⇒ Drug-induced SLE ⇒ IgA nephropathy ⇒ HOCM 	
HLA- B27	 Ankylosing spondylitis Post-gonococcal arthritis Reiter's syndrome (reactive arthritis) Acute anterior uveitis 	
HLA- DR3	 Autoimmune hepatitis Primary biliary cirrhosis Coeliac disease (95% associated with HLA-DQ2) Diabetes mellitus type 1 Primary Sjögren syndrome Dermatitis herpetiformis 	

Cluster of Differentiation (CD Markers)

Function and usage of CDs:

- The CD system is commonly used as cell markers in **immuno-phenotyping**, allowing cells to be defined based on what molecules are present on their surface.
- often acting as **receptors** or ligands (the molecule that activates a receptor)
- **cell signaling:** Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and DM
- Cell adhesion: essential for the pathogenesis of infectious organisms, eg:
 - ⇒ HIV has an adhesion molecule termed <u>ap120</u> that binds to its ligand CD4, which is expressed on lymphocyte.

The table below lists the major clusters of differentiation (CD) molecules

Cluster of differentiation	Function
CD1	MHC molecule that presents lipid molecules
CD2	Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion
CD3	The signalling component of the T cell receptor (TCR) complex
CD4	Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells
CD5	Found in the majority of mantle cell lymphomas
CD8	Found on cytotoxic T cells. Co-receptor for MHC class I Found on a subset of myeloid dendritic cells
CD14	Cell surface marker for macrophages
CD15	Expressed on Reed-Sternberg cells (along with CD30)
CD 21	Epstein-Barr virus uses the CD21 receptor to invade B cells.
CD28	Interacts with B7 on antigen presenting cell as costimulation signal
CD95	Acts as the FAS receptor, involved in apoptosis

Clusters of differentiation

- CD4
 - ⇒ Found on helper T cells.
 - ⇒ Co-receptor for MHC class II
 - ⇒ Used by HIV to enter T cells
 - GP120 \rightarrow fuses to CD4 \rightarrow allow GP41 to penetrate the cell membrane
- CD 8
 - ⇒ Found on cytotoxic T cells.
 - ⇒ Co-receptor for MHC class I
 - ⇒ Found on a subset of myeloid dendritic cells
- CD14 → Cell surface marker for macrophages
- CD18 → the absence of it causes Leukocyte adhesion deficiency

GP41 play a role in the initial step for HIV entry into cells

Gp120 fuses to the CD4 receptor, this then allows GP41 to penetrate the cell membrane

Complement pathways

- · Activation may occur via three pathways:
 - 1. Classical pathway:
 - Activated by IgM or IgG complexes binding to the pathogen
 - C1q, C1r, and C1s activation → C1 complex → split of C4 into C4a and C4b and C2 into C2a and C2b → formation of C3 convertase (C4b2b) from C4b and C2b
 - C2 is involved in activation via the classical pathway

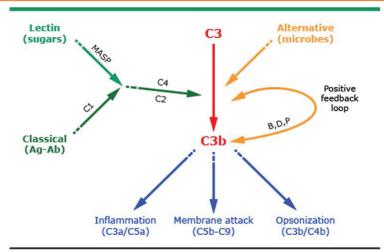
2. Alternative pathway:

- Activated directly by pathogen surface molecules rather than by antigenantibody complexes
- C3 is split into C3a and C3b → binding of factor B → formation of C3 convertase (C3bBb).
- Generates early innate response that does not require antibody for activation.

3. Lectin pathway:

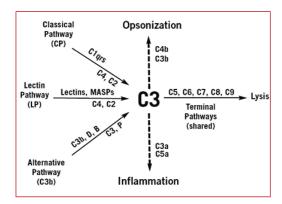
- Activated by mannose or other sugars on pathogen surface
- Mannose-binding lectin (MBL) binds to mannose → formation of the C1-like complex, which cleaves C4 into C4a and C4b → C4b binding C2 and splitting of C2 into C2a and C2b → formation of C3 convertase (C4b2b).
- All complement pathways have one final common pathway at C3.

IgG and IgM activate the classic pathway



The three pathways of complement activation are shown. Each leads to generation of activated C3b. The classical pathway is triggered by antibody interacting with antigen, and the lectin pathway by a lectin binding to a sugar. The alternative pathway turns over continuously. Activation of the complement system leads to inflammation (release of anaphylatoxins C3a and C5a), membrane perturbation and lysis (via the membrane attack complex, C5b-9), and opsonization (deposition of C3b and C4b).

MASP: mannose-binding lectin (MBL)-associated serine protease.



Hypersensitivity

The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types:

Туре	Mechanism	Examples
Type I - Anaphylactic	Antigen reacts with IgE bound to mast cells (IgE-mediated)	Anaphylaxis Atopy (e.g. asthma, eczema and hayfever) Diagnosed by plasma tryptase (protease released from mast cell).
Type II - Cell bound	lgG or IgM binds to antigen on cell surface (antibody- mediated)	 Autoimmune haemolytic anaemia ITP Goodpasture's syndrome Pernicious anaemia Acute haemolytic transfusion reactions Rheumatic fever Pemphigus vulgaris / bullous pemphigoid
Type III - Immune complex	Free antigen and antibody (IgG, IgA) combine (Immune complex deposition)	Serum sickness Systemic lupus erythematosus Post-streptococcal glomerulonephritis Extrinsic allergic alveolitis (especially acute phase)
Type IV - Delayed hypersensitivity	T-cell mediated (cell-mediated)	Tuberculosis / tuberculin skin reaction Graft versus host disease Allergic contact dermatitis Scabies Extrinsic allergic alveolitis (especially chronic phase) Multiple sclerosis Guillain-Barre syndrome

In recent times a further category has been added:

Туре	Mechanism	Examples
Type V	Antibodies that recognise and bind to the cell surface receptors. This either stimulating them or blocking ligand binding	• GraVes' disease • Myasthenia graVis

What is the hallmark signs of mast cell degranulation?

Classical wheal and flare

Anaphylaxis

Anaphylaxis = type I hypersensitivity reaction

Anaphylaxis - serum tryptase levels rise following an acute episode

Definition

 a severe type 1 hypersensitivity reaction that can cause life-threatening and multisystem effects due to IgE-mediated mast cell activation

Pathophysiology

- Immunoglobulin E is the most common immunoglobulin involved in the pathogenesis of anaphylaxis.
- Anaphylaxis (type I hypersensitivity reaction) or anaphylactoid reactions → degranulation of
 mast cells → massive histamine release → systemic vasodilation → increased capillary
 leakage → anaphylactic shock
- Mediators involved in the development of anaphylaxis include: Tryptase, histamine, leukotrienes, prostaglandins, IL4, IL13, Heparin and platelet aggregating factor, which are generated by mast cell degranulation.
- Triggers for anaphylactic reactions: heat, cold, sexual activity, exercise

Causes

- 1. Anaphylaxis (IgE mediated):
 - ⇒ Food (e.g. Nuts) the most common cause in children
 - ⇒ Drugs
 - The most common IgE-mediated triggers are drugs, typically penicillin or other beta-lactam antibiotics.
 - Neuromuscular blocking agents (eg vecuronium) are responsible for 60-70% of allergic reactions related to anaesthesia.
 - ⇒ Latex
 - ⇒ Venom (e.g. Wasp sting)
- 2. Anaphylactoid (non-lgE mediated).
 - ⇒ The reactions that produce the same <u>clinical picture</u> as anaphylaxis <u>but are not</u> <u>lqE mediated</u>.'
 - plasma proteins or compounds, which act directly on the mast cell membrane, such as
 - Vancomycin

- Quinolone antibiotics
- Aspirin or other non-steroidal anti-inflammatory drugs
- Opiates
- Colloid plasma expanders
- Radiographic contrast media

Anaphylaxis following a blood transfusion can be due to immunoglobulin A deficiency.

Anaphylaxis VS Anaphylactoid

Is it anaphylactic OR anaphylactoid reaction?

	Anaphylactic (IgE-mediated anaphylactic reactions)	Anaphylactoid (Non IgE-mediated anaphylactic reactions)
Is sensitization required?	Yes	No
Can reaction occur in first exposure?	No	Yes
How much exposure is needed to elicit reaction?	very little (dose independent)	usually more than for anaphylaxis
Is reaction predicted by skin allergy test?	Yes	No

Which feature is the most important predictor of anaphylaxis in asthmatic patient with peanut allergy?

- Poorly controlled asthma
 - Poorly controlled asthma is an important risk factor for fatal anaphylaxis in this situation.
 - Patients such as this should have their asthma well controlled and have ready access to, and knowledge of how to use, self-injectable adrenaline.

Features (Usually takes 15-30 minutes from the time of exposure to the antigen)

- Skin or mucous membranes: Flushing, erythema, pruritus, Swelling of the eyelids, angioedema
- **Respiratory:** hoarseness, Chest tightness, Dyspnea (due to bronchospasm or laryngeal edema), tachypnea, Stridor, wheezing, Hypoxia, cyanosis
- Gastrointestinal: Nausea, vomiting (especially in food allergies), Abdominal pain, diarrhea
- Cardiovascular: Hypotension, Tachycardia

Investigations

- Serum mast-cell tryptase: if elevated, supports the diagnosis of anaphylaxis
 - ⇒ has a half-life of 2 h, peaking at 1 h after anaphylaxis onset and return to baseline by 6 hours.
 - ⇒ Both sensitivity and specificity to confirm diagnosis is 95%
 - ⇒ Normal tryptase results do not exclude anaphylaxis
- Complement C4 levels: can be low in hereditary angioedema
- Total serum IgE level is non-specific and unhelpful.

Management

- Airway assessment and management: Rapid sequence intubation (RSI) for airway compromise
- Adrenaline
 - ⇒ the most important drug in anaphylaxis and should be given as soon as possible.
 - ⇒ The dose for adult and child > 12 years : 500 micrograms (0.5ml 1 in 1,000)
 - ⇒ The best site for IM injection is the anterolateral aspect of the middle third of the thigh.
 - ⇒ Adrenaline can be repeated every 5 minutes if necessary.
- Hydrocortisone 200 mg
- Chlorphenamine 10 mg
- IV fluids
 - ⇒ Evidence from a large randomised controlled trial (RCT) suggests there is no difference between normal saline and Hartmann's solution [also known as Ringer's lactate] for resuscitation of critically ill patients.
- Observation: It is recommended to observe patients after resolution of an anaphylactic episode for 24 hours **for possible second-phase reactivation**.

Late-phase reaction

In IgE mediated reactions such as asthma or anaphylaxis what therapy inhibits the important late-phase reaction? steroids

- The late phase reaction is due to attraction of T cell, release of leukotrienes and prostaglandins often characterised by asthma
- prevented by the administration of steroids (Hydrocortisone).
- Approximately 30% of deaths related to anaphylaxis occur as a consequence of this late-phase reaction

Epinephrine injections for anaphylaxis should always be given intramuscularly in a concentration of 1:1,000 (as opposed to the 1:10,000 solution used in cardiac arrest). Injecting the 1:1,000 solution into a vein can lead to cardiac arrhythmia/arrest.

Antihistamines and steroids should be administered in anaphylaxis only after the initial resuscitation measures (IM epinephrine, fluids and/or vasopressors) have been given.

A lack of response to epinephrine, antihistamines, and steroids should raise suspicion of differential diagnoses such as bradykinin-mediated angioedema, which requires its own specific treatment

Exercised induced anaphylaxis

Definition

• a rare disorder in which anaphylaxis occurs after physical activity.

Features

 usually occur around 10 minutes after exercise and follow a sequence of pruritus, widespread urticaria and then subsequently respiratory distress and vascular collapse.

Pathophysiology

 may be related to endorphin release during exercise → excessive histamine release from mast cells in susceptible individuals.

Associations

- Co-factors such as foods, alcohol, temperature, drugs (eg, aspirin and other nonsteroidal anti-inflammatory drugs), humidity, seasonal changes, and hormonal changes are important in the precipitation of attacks.
- most associated with wheat ingestion.
- The foods most commonly implicated in food-dependent exercise-induced anaphylaxis are wheat, shellfish, tomatoes, peanuts, and corn.
- The patients can usually eat the causative food without problems so long as they do not exercise afterwards.

Treatment

- managed in the same manner as anaphylaxis.
- · usually resolves on stopping exercise
- Reducing physical activity to a lower level may diminish the frequency of attacks.
- Patients should be instructed on the proper use of emergency injectable epinephrine and have one available at all times.
- Patients should wear a medical alert bracelet with instructions on the use of epinephrine.

Anaphylactic reactions associated with anaesthesia

Risk factors

- Neuromuscular blocking drugs and latex appear to cause anaphylaxis more commonly in female patients
- Individuals with a history of atopy, asthma or allergy to some foods appear to be at increased risk of latex allergy but not anaphylaxis to neuromuscular blocking drugs or antibiotics
- Patients with asthma or taking b-blocking drugs may suffer a more severe reaction.

Causes

- Neuromuscular blocking agents (NMBAs)
 - ⇒ Most common cause
 - ⇒ 60% of cases of anaesthesia-related anaphylaxis are due to neuromuscular blocking agents.
 - ⇒ 80% of NMBA reactions occur without prior exposure
 - Quaternary ammonium ions (QAI) are proposed to be the allergenic epitopes in NMBAs.
 - Common environmental chemicals such as toothpastes, washing detergents, shampoos, and cough medicines share these allergenic epitopes with the NMBAs, predisposed individual to become sensitised to QAIs and thus be at <u>risk of developing anaphylaxis to NMBAs during anaesthesia.</u>
 - succinylcholine is the NMBA most likely to be associated with allergic anaphylaxis (carries the highest risk)

Latex

⇒ Latex hypersensitivity is the second most common cause of anaesthesia related anaphylaxis in many studies (up to 20% of cases). But now decreased due to decline in the use of latex gloves.

Antibiotics

- ⇒ Approximately 15% of anaesthesia-related anaphylactic episodes are due to antibiotics.
 - Skin testing is only approximately 60% predictive of clinical hypersensitivity.
 Penicillins and

- cephalosporins which share the b-lactam ring are responsible for approximately 70% of antibiotic-induced anaphylaxis.
- There is a higher rate of antibiotic allergy in smokers
- Anaesthetic induction agents
 - ⇒ Anaphylaxis to propofol is very uncommon
 - ⇒ Anaphylaxis to thiopental has become extremely uncommon, probably reflecting the decline in its use.
- Antiseptics and disinfectants
 - Reactions to **chlorhexidine** have come into greater prominence in recent years.
 - ⇒ Anaphylaxis has occurred when chlorhexidine was used as an antiseptic for urological and gynaecological procedures as well as insertion of central venous and epidural catheters.
 - Allowing chlorhexidine to dry before beginning a procedure may reduce the risk of reaction.
 - ⇒ Anaphylaxis to other antiseptics is rare.

Diagnosis

- Timings
 - ⇒ Type I reactions typically occur within **seconds to minutes** after **i.v. exposure**.
 - ⇒ An insidious or delayed onset may occur (e.g. with latex, antibiotics, and colloids and a tourniquet may delay onset until after surgery).
- History of atopy and asthma has a clear link with latex allergy.

Allergy tests	
Skin prick test	 Most commonly used test as an easy to perform and inexpensive. the first line for detection of allergen-specific IgE Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle. A large number of allergens can be tested in one session. Normally includes a histamine (positive) and sterile water (negative) control. A wheal will typically develop if a patient has an allergy. Can be interpreted after 15 minutes Useful for food allergies and also pollen. It is a reliable way of excluding IgE-mediated food allergies, although the positive predictive value is around 50% or less (the sensitivity of a negative skin prick test to foods is high) It can induce anaphylaxis, and must therefore be done in an environment where resuscitation facilities are available.
Radioallergosorbent test (RAST)	 Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein. Results are given in grades from 0 (negative) to 6 (strongly positive) Useful for food allergies, inhaled allergens (e.g. Pollen) and wasp/bee venom Blood tests may be used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines
Skin patch testing	 Useful for contact dermatitis. Around 30-40 allergens are placed on the back. Irritants may also be tested for. The patches are removed 48 hours later with the results being read by a dermatologist after a further 48 hours

If a history of anaphylaxis is given it would not be appropriate to perform a skin prick test, thus Radioallergosorbent test (RAST) is the most appropriate first-line test to investigate the cause of the reaction

Reasons for a false negative RAST test

- Immediately following anaphylaxis / allergic reaction (transient drop in IgE)
- Waning of allergen-specific IgE with time following a reaction.
- Unstable allergens in the RAST substrates (especially food allergens)

Only IgE-mediated allergic reactions can be tested by skin prick testing

The wheal size resulting from the skin prick test is an excellent predictor of a positive food challenge to peanuts

Latex allergy

Definition

- A type I or type IV hypersensitivity to latex-based products (e.g., exam gloves, condoms) **Epidemiology**
 - 8–12% of health care workers are affected
 - NHS trusts in the UK have moved away from the routine use of latex gloves precisely because of the risk of allergy. As a result, latex allergy in hospital is now very rare in the UK.
 - Latex allergy is more common in children with myelomeningocele spina bifida.

Pathophysiology |

- Sensitivity to latex may cause several problems:
 - ⇒ type I hypersensitivity (anaphylaxis)
 - it is very unlikely that a latex allergy would explain an anaphylaxis during anaesthetic induction (latex allergies typically used to commence when a surgeon began handling internal organs).
 - ⇒ type IV hypersensitivity (allergic contact dermatitis)
 - Type 4 hypersensitivity is usually due to accelerators or chemicals used in the manufacturing process, whereas type 1 hypersensitivity is due to the latex proteins themselves
 - ⇒ irritant contact dermatitis

Latex-fruit syndrome

 It is recognised that many people who are allergic to latex are also allergic to fruits, particularly banana, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry. However, bananas are the most commonly associated with latex/rubber allergy

Latex allergy can be associated with certain foods such as bananas, avocado, kiwi and melon.

MRCPUK part-1-May 2016 exam: A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed? Banana

Serum Sickness

Definition

Serum sickness is a classic example of a type III hypersensitivity reaction, which usually
develops as a complication of antitoxin or antivenom administration.

Aetiology

- Antivenom or antitoxin containing animal proteins
- Medications most frequently antibiotics (e.g., penicillin, amoxicillin, cefaclor, trimethoprimsulfamethoxazole)
- Infections: Hepatitis B virus

Pathophysiology

 exposure to an antigen (e.g., antivenom, drug) → formation of antibodies → deposition of antibody-antigen complexes in tissue → activation of the complement cascade → tissue damage and systemic inflammation

Features

- Symptoms appear 1–2 weeks following initial exposure (because antibodies take several
 days to form), and usually resolve within a few weeks after discontinuation of the offending
 agent.
- Fever
- Rash (urticarial or purpuric)
- Arthralgias
- Lymphadenopathy

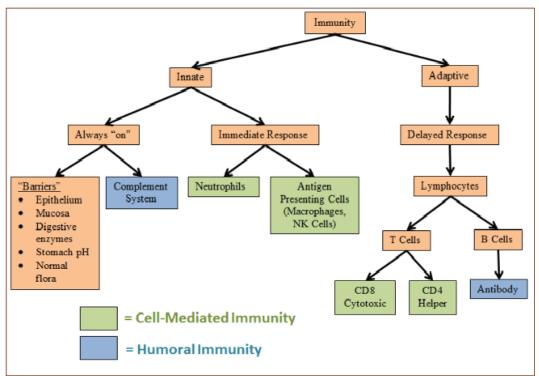
Subtypes and variants: serum sickness-like reaction

- much more common than actual serum sickness
- · Aetiology: similar to that of serum sickness
- Infections (e.g., hepatitis B, rabies)
- Medications that can act as haptens (e.g., allopurinol, cephalosporins, penicillin).

Diagnostics: Urinalysis may show mild **proteinuria**.

Treatment: Stop the offending agent.

Immune system response



Innate VS Adaptive immune response

Innate (non-specific system)	Adaptive (acquired system)
Components 1. Anatomical and physiological barriers 2. Inflammatory response with leakage of antibacterial serum proteins (acute-phase proteins) and phagocytic cells 3. Phagocytosis by neutrophils and macrophages 4. Complement system	Components 1. Cell-mediated response effected by T cells 2. Humeral immune response effected by B cells
Properties 1. Rapid: responds within minutes to infection 2. No antigenic specificity, i.e. the same molecules and cells respond to range of pathogens 3. No memory, i.e. the response does not change after repeated exposure 4. Preformed or rapidly formed components	Properties 1. Slow: response over days to weeks 2. Antigenic specificity i.e. each cell is a programmed genetically to respond to a single antigen 3. Immunological memory, i.e. on repeated the response is faster, stronger and qualitatively different 4. Diversity: ability to recognize and respond to a vast number of different antigens 5. Self/non-self-recognition: i.e. lack of response (tolerance) to self-antigens but response to foreign antigens

Overview of blood cell types involved in the innate immune response

Cell type	Functions and properties
Neutrophil	 Primary phagocytic cell in acute inflammation Granules contain myeloperoxidase and lysozyme Most common type of white blood cell Multi-lobed nucleus
Basophil	 Releases histamine during allergic response Granules contain histamine and heparin Expresses IgE receptors on the cell surface Bi-lobed nucleus
Mast cell	 Present in tissues and are similar in function to basophils but derived from different cell lines Granules contain histamine and heparin Expresses IgE receptors on the cell surface
Eosinophil	Defends against protozoan and helminthic infectionsBi-lobed nucleus
Monocyte	Differentiates into macrophagesKidney shaped nucleus
Macrophage	 Involved in phagocytosis of cellular debris and pathogens Acts as an antigen presenting cell Major source of IL-1
Natural killer cell	⊃ Induce apoptosis in virally infected and tumour cells
Dendritic cell	⇒ Acts as an antigen presenting cell, but have no cytotoxic potential.

Macrophages

Overview

- Macrophages are a type of antigen-presenting cell, defined as a lymphocyte that is able to phagocytose debris, toxins, cells or pathogens.
- Origin: Monocytes migrate to tissue and differentiate into macrophages.
- Activated by y-interferon.
- Has a long life in tissues, which differentiates it from a circulating blood monocyte
- Important cellular component of granulomas (eg, TB, sarcoidosis), where they may fuse to form giant cells.

Tissue-specific subtypes

- Osteoclasts (bone)
- Kupffer cells (liver)
- Microglia (brain and spinal cord)
- Histiocytes (connective tissue)

A patient undergoes liver biopsy, which shows ↑ phagocytes with kidney-shaped nuclei. What are these cells called?

⇒ Kupffer cells (the names of macrophages can differ in each tissue)

What signaling molecule activates macrophages?

⇒ y-interferon

Important macrophage forms in various Diseases

- Lipid laden macrophage (Foam cells) = Hyperlipidemia & Atherosclerotic plaques.
- Hemosiderin laden macrophage(Heart failure cells) = CHF.
- Macrophages containing debris from ingested Lymphocytes (Tingible body macrophage) = Benign reactive lymphadenitis.
- Macrophages containing PAS +ve, gram +ve rod shaped bacilli within Lamina propria in small intestine = Whipple Disease.
- Iron trapped in Macrophages in Bone marrow = Anemia of chronic disease.
- Macrophages containing Carbon pigment along pleural lymphatics = Anthracosis.
- Tissue paper like macrophage = Gaucher disease.

The lipid A component of bacterial lipopolysaccharide (LPS) binds to CD14 on macrophages, which can trigger septic shock

Pathogenesis of atherosclerosis

- 1. Chronic stress on the endothelium
- 2. Endothelial dysfunction, which leads to
 - Invasion of inflammatory cells (mainly monocytes and lymphocytes) through the disrupted endothelial barrier
 - Adhesion of platelets to the damaged vessel wall → platelets release inflammatory mediators (e.g., cytokines) and platelet-derived growth factor (PDGF)
 - ◆ PDGF stimulates migration and proliferation of smooth muscle cells (SMC) in the tunica intima and mediates differentiation of fibroblasts into myofibroblasts
- 3. Inflammation of the vessel wall
- Macrophages and SMCs ingest cholesterol from oxidized LDL and transform into foam cells.
- **5.** Foam cells accumulate to form fatty streaks (early atherosclerotic lesions).
- Lipid-laden macrophages and SMCs produce extracellular matrix (e.g., collagen) → development of a fibrous plaque (atheroma)
- 7. Inflammatory cells in the atheroma (e.g., macrophages) secrete matrix metalloproteinases

 → weakening of the fibrous cap of the plaque due to the breakdown of extracellular matrix

 → minor stress ruptures the fibrous cap
- 8. Calcification of the intima (the amount and pattern of calcification affect the risk of complications)
- 9. Plaque rupture → exposure of thrombogenic material (e.g., collagen) → thrombus formation with vascular occlusion or spreading of thrombogenic material

Foam cells

- Foam cells are a feature of atherosclerotic plaques and are essentially lipid-laden macrophages.
- They may also be seen as a reaction to:
 - ⇒ silicone leakage around breast implants, and
 - ⇒ inhaled organic antigens.

MRCPUK exam- Jan-2018: You are examining tissue biopsied from around a leaking silicone breast implant. It is rich in foam cells. What is the cell lineage of foam cells?

Macrophage

Fibroblasts

- The most common cell type in connective tissue
- Origin: derived from mesenchymal stem cells
- Found in the interstitial spaces of organs.
- Histological features: spindle-shaped cells arranged in a branching pattern
- Function:
 - ⇒ synthesis and organization of the extracellular matrix (ECM) and collagen
 - ⇒ plays a critical role in wound healing
 - ⇒ play a critical role in an immune response to a tissue injury.
 - ⇒ They are <u>early players in initiating inflammation</u> in the presence of invading microorganisms. Tissue damage stimulates fibrocytes and induces the mitosis of fibroblasts.
 - ⇒ Responsible for forming the cap over an atherosclerotic plaque.
- Pathologic fibrosis is characterized by uncontrolled fibroblast activation that results in exaggerated and persistent ECM accumulation and remodeling.

<u>Immunoglobulins</u>

IgD is involved in the activation of B-cells

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

body:			
Type	Frequency	Shape	Notes
IgG	75%	Monomer	comprises the majority of circulating antibody in serum the major antibody produced in the secondary immune response. Enhance phaGocytosis of bacteria and viruses half-life: 7-23 days Fixes classical complement can bind to NK cells for antibody-dependent cytotoxicity (ADCC). the only antibody that can cross the placenta and enter the fetal circulation Most abundant isotype in blood serum Gamma is the type of heavy chain found in IgG.
lgA	15%	Monomer/ dimer	 Found in secretions such as saliva, tears and mucous made primarily in the mucosal-associated lymphoid tissues (MALT). Provides localized protection on mucous membranes The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes. Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG) half-life ≈ 5 days Transported across the interior of the cell via transcytosis can activate the <u>alternative</u> complement pathway. (IgA ≈ Alternate) Low levels of IgA are associated with an increased incidence of Coeliac Disease. Alpha is the type of heavy chain found in IgA.

Туре	Frequency	Shape	Notes
IgM	10%	Pentamer	 First immunoglobulins to be secreted in response to an infection (primary response) Fixes <u>classical</u> complement pathway (most efficient) Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis) Monomeric forms of IgM are found on the surface of B-lymphocytes as B-cell receptors or slg. half-life: about 5 days Mu is the type of heavy chain found in IgM.
lgD	1%	Monomer	 Involved in activation of B cells (as a surface receptor on B cells) may play a role in eliminating B-lymphocytes generating self-reactive autoantibodies. Delta is the type of heavy chain found in IgD. Hyper-IgD is associated with periodic fever (attacks of fever every 4-8 weeks, with each attack lasting 3-7 days)
IgE	0.1%	Monomer	 produced by plasma cells Mediates type 1 hypersensitivity reactions Binds to Fc receptors found on the surface of mast cells and basophils Provides immunity to parasites such as helminths Least abundant isotype in blood serum half-life of 2 days IgE may protect external mucosal surfaces by promoting inflammation, enabling IgG, complement proteins, and leucocytes to enter the tissues. Cross linking of cell-bound IgE by antigen triggers the release of vasodilators for an inflammatory response. The Fc portion of IgE made against parasitic worms and arthropods can bind to eosinophils enabling opsonization. This is a major defense against parasitic worms and arthropods. Epsilon is the type of heavy chain found in IgE. Raised IgE levels are a normal finding in 2.5%

Each day an average adult produces approximately 3gm of antibodies, about two-thirds of this IgA

Acute organ rejection is due to anti-IgG antibodies to the human leukocyte antigen (HLA) incompatible tissues with primary activation of T cells.

Blood transfusion

Rhesus antibodies are IgG, whereas ABO antibodies are IgM

Commonly recognized immunoglobulin changes in liver disease

(usually accompanied by a decrease in albumin) are:

- **IgG** ↑ in: chronic active hepatitis, cryptogenic cirrhosis
- IgM ↑ in: 1° biliary cirrhosis, alcoholic cirrhosis
- IqA ↑ in: alcoholic cirrhosis.

Immunoglobulins (antibodies) have two functional parts: the Fc region and the Fab region

- Fc region
 - ⇒ Contains the **constant** region
 - ⇒ Formed by **heavy** (H) chains
 - ⇒ Recognizes and binds **complement** (IgG, IgM)
- Fab region
 - ⇒ Contains the variable region
 - ⇒ Formed by light (L) chains and heavy (H) chains
 - ⇒ Recognizes and binds to antigens

Immunoglobulins and complement fixation

- IgA can fix complement via the alternative pathway
- IgG and IgM can fix complement via the classical pathway through the Fc portion of the immunoglobulin

Protein analysis: Gamma globulins

- Hypergammaglobulinaemia
 - ⇒ Causes of polyclonal hypergammaglobulinaemia
 - Artefactual, e.g. prolonged venous stasis before venepuncture
 - Haemoconcentration secondary to dehydration
 - Chronic infection, e.g. TB, infective endocarditis, leishmaniasis
 - Autoimmune disease, e.g. SLE, rheumatoid arthritis
 - Ulcerative colitis and Crohn's disease
 - Sarcoidosis
 - Hepatic disease.

⇒ Causes of monoclonal hypergammaglobulinaemia

- Multiple myeloma, Waldenstrom's macroglobulinaemia and heavy chain disease
- Leukaemia, lymphoma or carcinoma
- Bence Jones proteinuria
- 'Benign' paraproteinaemia
- Amyloidosis.
- Agammaglobulinemia (e.g., Bruton agammaglobulinemia)
- Hypogammaglobulinemia (low lgG)
 - ⇒ Nephrotic syndrome
 - ⇒ Drug-induced reactions
 - ⇒ Acquired humoral and congenital immunodeficiencies

Immunoglobulins: therapeutics

Basics

- formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- half-life of 3 weeks

Uses

- primary and secondary immunodeficiency
- · idiopathic thrombocytopenic purpura

- myasthenia gravis
- · Guillain-Barre syndrome
- Kawasaki disease
- toxic epidermal necrolysis
- pneumonitis induced by CMV following transplantation
- low serum IgG levels following haematopoietic stem cell transplant for malignancy
- dermatomyositis
- chronic inflammatory demyelinating polyradiculopathy

Leukotrienes

Overview

- · mediators of inflammation and allergic reactions
- · secreted by leukocytes
- · formed from arachidonic acid by action of lipoxygenase
- it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase

Function

- · cause bronchoconstriction.
- mucous production (an important consideration in the pathophysiology of bronchial asthma)
- increase vascular permeability, attract leukocytes
- leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)
 which causes bronchial wall and intestinal smooth muscle contraction

Acute phase proteins

Acute phase proteins

- CRP
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- · serum amyloid A, serum amyloid P
- haptoglobin
- complement

Negative acute phase proteins

- During the acute phase response, the **liver decreases the production of other proteins** (sometimes referred to as negative acute phase proteins). Examples include:
 - ⇒ albumin
 - ⇒ transthyretin (formerly known as prealbumin)
 - ⇒ transferrin
 - ⇒ retinol binding protein
 - ⇒ cortisol binding protein

ANCA

cANCA = Wegener's; pANCA = Churg-Strauss + others

- There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA):
 - 1. cytoplasmic (cANCA) and
 - 2. perinuclear (pANCA)
- For the exam, remember:
 - ⇒ cANCA Wegener's granulomatosis
 - ⇒ pANCA Churg-Strauss syndrome + others (see below)

cANCA

- most common target serine proteinase 3 (PR3)
- · some correlation between cANCA levels and disease activity
- Wegener's granulomatosis, positive in > 90%
 - ⇒ In Wegener's, the level of PR3 antibody and ANCA titre are related to disease activity and the antibodies typically disappear when the disease is in remission.
- microscopic polyangiitis, positive in 40%

pANCA

- most common target is myeloperoxidase (MPO)
- cannot use level of pANCA to monitor disease activity
- associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- primary sclerosing cholangitis, positive in 60-80%
- Wegener's granulomatosis, positive in 25%
- Other causes of positive ANCA (usually pANCA)
 - ⇒ inflammatory bowel disease (UC > Crohn's)
 - ⇒ connective tissue disorders: RA, SLE, Sjogren's
 - ⇒ autoimmune hepatitis

MRCP-part-1-Jan-2018 exam: Which one of the following statements is true regarding cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA)?

• Associated with Wegener's granulomatosis

Rheumatoid factor (see rheumatology)

Antibodies and immunological markers

Marker	Associated condition	
Antinuclear	Younger women often have low (ANAs)	
antibodies (ANA)	increase with age	
	 ANA positivity with antiphospholipid antibody syndrome (APL) suggests secondary APL, ie in association with a connective tissue disease. 	
	 The common tests used for detecting and screening ANAs are indirect immunofluorescence and enzyme-linked 	

Marker	Associated condition
	 immunosorbent assay (ELISA). Although positive titres of 1:160 or higher are strongly associated with autoimmune disorders, they are also found in 5% of healthy individuals Positive titres of less than 1:160 are present in up to 20% of the healthy population, especially the elderly.
Anti-Ro (SS-A) and anti-La (SS-B)	Anti-Ro Sjögren's syndrome (50–70%) SLE with cutaneous involvement (30%) anti-Ro can cross the placenta and cause neonatal lupus in babies.
Anti-Smith (Anti-Sm)	very specific marker for SLE (99%) sensitivity (20%) not associated with disease activity.
Anti-nuclear ribonucleoprotein (anti-nRNP) also known as anti-U1- RNP	highly associated with mixed connective tissue disease . SLE (30 – 40%)
Anti-double stranded DNA (anti-dsDNA)	very specific marker for SLE, (nearly 100%). sensitivity (85%). Correlate with disease activity in SLE. also linked with lupus nephritis.
Anti-histone	drug induced lupus (75–95%) idiopathic SLE (75%) Unlike anti-dsDNA, these antibodies do not fix complement.
anti-glycoprotein- 210 (anti-gp210) and anti-nucleoporin 62 (anti-p62)	primary biliary cirrhosis (PBC) (25–30%).
Anti-centromere	limited cutaneous systemic sclerosis, also known as CREST syndrome, primary biliary cirrhosis
Thyroid autoantibodies (microsomal and thyroglobulin)	Hashimoto's thyroiditis (70-90% microsomal: 75-95% thyroglobulin) Pernicious anaemia (55% microsomal)
Anti-Scl-70	diffuse cutaneous scleroderma (40%), limited cutaneous involvement (10%). SLE (5%) The antigenic target of anti-Scl-70 antibodies is topoisomerase I
Antireticulin	Coeliac disease (37%) Crohn's disease (24%)
Gastric parietal cell antibody	Pernicious anaemia (>90%) Atrophic gastritis(60%) Autoimmune thyroid disease (33%)

Marker	Associated condition	
Anti-mitochondrial	Primary biliary cirrhosis (60-94%)	
antibody	,,	
Anti-smooth muscle	Chronic active hepatitis (40-90%)	
antibody	Primary biliary cirrhosis (30-70%)	
_	Idiopathic cirrhosis (25-30%)	
	Viral infections (80%)	
Anti-sp100	primary biliary cirrhosis (PBC) (20-30%).	
-	very specific marker of the disease.	
Anti-PM-ScI	polymyositis/systemic sclerosis (PM/SSc) overlap syndrome (50%).	
Anti-Hu	small-cell lung cancer, neuroblastoma and prostatic cancer	
Intrinsic factor antibodies	pernicious anaemia, and hence (subacute combined degeneration of the spinal cord) secondary to vitamin B12 deficiency	
Anti-Ri	neuroblastoma (children) and fallopian or breast cancer (adults), resulting in paraneoplastic opsoclonus myoclonus ataxia (POMA).	
Anti-Yo	gynaecological tumours and breast cancer,	
Anti-Tr	Hodgkin's disease, resulting in cerebellar degeneration.	
Anti-Ta (Ma2)	testicular tumours, and can lead to limbic or brain stem encephalomyelitis.	
Anti-endomysial /	coeliac disease, and related vitamin B-1 deficiency may lead to	
gliadin /	Wernicke's encephalopathy and Korsakoff's psychosis	
transglutaminase		
Tissue	The most accurate blood tests for coeliac disease	
transglutaminase antibody ('tTGA')		
& Endomysial		
antibody ('EMA')		
double-stranded	highly specific for SLE.	
DNA (ds-DNA) Anti-		
dsDNA		
Antibodies that bind	present in 90% of patients with SLE, but also in drug-induced lupus and	
single-stranded	other connective tissue disorders.	
denatured DNA (ss- DNA)		
Anti-Jo	Polymyositis	
Rheumatoid factor	Rheumatoid arthritis, Sjogren's (90%), SLE (30%)	
	5% of normal population	

The only two auto-antibodies which have a role in monitoring disease activity (there is correlation between levels and disease activity)

- 1. Anti-ds DNA antibodies in systemic lupus erythematosus (SLE)
- 2. Circulating anti-neutrophil cytoplasmic antibody (cANCA) in Wegener's granulomatosis.

Interleukins

Definition

• Interleukin are a group of signaling proteins expressed by leukocytes that regulate immune response as well as cellular proliferation and differentiation.

Production

 The majority of interleukins are synthesized by helper CD4 T lymphocytes, as well as through monocytes, macrophages, and endothelial cells.

Function

- The function of the immune system depends in a large part on interleukins,
- They promote the development and differentiation of T and B lymphocytes, and hematopoietic cells.

Both cytokine overexpression and underexpression can be pathogenic:

- Production of IL-1, IL-6 and TNF due to endotoxin stimulation of macrophages following Gram-negative infection → Septic shock
- Chagas' disease (Trypanosoma cruzi infection) → reduced expression of IL-2 receptor → marked immune suppression.

Overview of interleukins

Cytokine	Main sources	Functions
IL-1	Macrophages	Acute inflammation Induces fever
IL-2	Th1 cells	Stimulates growth and differentiation of T cell response
IL-3	Activated T helper cells	Stimulates differentiation and proliferation of myeloid progenitor cells
IL-4	Th2 cells	Stimulates proliferation and differentiation of B cells (Stimulates switching to IgE and IgG .)
IL-5	Th2 cells	Stimulates proliferation and differentiation of B cells (Stimulates switching to IgA .) Stimulate production of eosinophils
IL-6	Macrophages, Th2 cells	Stimulates differentiation of B cells Induces fever stimulates production of acute phase proteins.
IL-8	Macrophages	Neutrophil chemotaxis
IL-10	Th2 cells	Inhibits Th1 cytokine production Also known as human cytokine synthesis inhibitory factor and is an 'anti-inflammatory' cytokine
IL-12	Dendritic cells, macrophages, B cells	Activates NK cells. stimulates differentiation of naive T cells into Th1 cells

Other cytokines

Cytokine	Main sources	Functions
Tumour necrosis factor-α	Macrophages	Induces fever Neutrophil chemotaxis
Interferon-y	Th1 cells	Activates macrophages

Mnemonic Hot T-Bone stEAk

- ⇒ IL-1: fever (Hot)
- ⇒ IL-2: stimulates T lymphocytes
- **□** IL-3: stimulates Bone marrow
- ⇒ IL-4: stimulates IgE
- ⇒ IL-5: stimulates IgA

Interleukin 1 (IL-1)

- Produced by macrophages and monocytes
- Action
 - ⇒ Endogenous pyrogen (one of the mediators of shock in sepsis): promotes
 - Fever (Along with **IL-6** and **TN**F, it acts on the hypothalamus causing **pyrexia**)
 - Vasodilation → edema
 - Adhesion and diapedesis of inflammatory cells via cytokines, e.g. WBCs
 - ⇒ Co-stimulator of T cell and B cell proliferation. (Stimulation of acute phase response)
 - ⇒ Hematopoietic growth factor
 - Stimulates proliferation of granulocytes in the bone marrow and lymphocytes in the spleen
 - Inhibits hematopoiesis
 - ⇒ Induces expression of adhesion molecules in the endothelium
 - ⇒ Promotes differentiation of Th17 cells involved in autoimmunity
 - ⇒ Also known as osteoclast-activating factor: Dysregulation of IL- 1 in cartilage leads to damage and osteoarthritis.
 - ⇒ Play a role in the formation of the atherosclerotic plaque
 - The uptake of oxidized low-density lipoproteins (LDL) by vascular endothelial cells results in → IL-1 expression → stimulates the production of plateletderived growth factor.

Interleukin-2 (IL-2)

- Produced by Th1 cells (mainly CD4+ cells)
- Functions
 - ⇒ Stimulates proliferation and differentiation of T cells (helper, cytotoxic, regulatory T cells, and natural killer cells)
 - ⇒ Activates macrophages
 - ⇒ IL-2 is part of the body's natural response to microbial infection, and in discriminating between foreign ("non-self") and "self".
 - ⇒ there is some evidence that IL-2 may be involved in itchy psoriasis
- Therapeutic use
 - ⇒ High-dose interleukin-2 can produce a high rate of response and durable remissions in patients with metastatic renal cancer.
 - ⇒ IL-2 analog (aldesleukin): metastatic melanoma and renal cell carcinoma
 - ⇒ IL-2 antagonists (e.g., basiliximab): prevention of renal transplant rejection

Interferon

Interferon-y is responsible for activating macrophages

To remember the use of interferon-y, think

"Interferon gamma for granulomatous diseases!"

Overview

- Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia.
- Are a part of the innate immune system
- · Have antiviral, antimicrobial, and antiproliferative properties
- Used in the treatment of chronic infections (hepatitis B and C, chronic granulomatous diseases), immune-mediated diseases (multiple sclerosis), and even tumors (leukemia, Kaposi sarcoma)
- They are classified according to cellular origin and the type of receptor they bind to.
- IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors.

Types

- IFN-alpha
 - ⇒ **Produced by** leucocytes
 - ⇒ **Function:** Antiviral action (Inhibits viral protein synthesis by activating ribonuclease L)
 - ➡ Therapeutic use: Hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer, hairy cell leukaemia
- IFN-beta
 - ⇒ **Produced by** fibroblasts
 - ⇒ **Function**: Antiviral action
 - ⇒ Therapeutic use: Multiple sclerosis → Reduces the frequency of exacerbations in patients with relapsing-remitting MS
- IFN-gamma (γ)
 - ⇒ The only member of the type II class of interferons
 - ⇒ **Produced by** Th1 cell
 - **⇒** Function
 - Activates macrophages to increase phagocytosis
 - Activates the expression of Class II major histocompatibility complex (MHC) molecules
 - Weaker antiviral action
 - ⇒ Therapeutic use
 - Chronic granulomatous diseases (e.g., leprosy, leishmaniasis, toxoplasmosis)

Side effects of interferon

- Flu-like symptoms (fever, chills)
- Depression
- Myopathy
- Neutropenia
- · Interferon-induced autoimmunity

What is the MOA of Toxic Shock Syndrome Toxin (TSST-1) from Staphylococcus aureus?

 Bringing of MHC II and T-cell receptors in proximity to outside of the antigen binding site, thereby causing overwhelming release of IFN-gamma and IL-2

The relation between IL-12 and IFN-gamma:

How do IFN-gamma levels change in IL-12 Receptor Deficiency?

- Decrease
 - IL-12 → Th1 cell activation → release IFN-gamma → activates macrophages.
 - No IL-12 action = no IFN-gamma release from Th1 cells

Tumour necrosis factor (TNF)

Overview

- Tumour necrosis factor (TNF) is a pro-inflammatory cytokine with multiple roles in the immune system
- TNF is secreted mainly by macrophages
- Act mainly in a paracrine fashion

Function

- Activates macrophages and neutrophils, acts as co-stimulator for T cell activation
- Increased acute phase proteins
- Similar properties to IL-1, induced pyrexia
- TNF is important in the pathogenesis of rheumatoid arthritis.
 - ⇒ TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid
- A key cytokine in the pathogenesis of multi-organ failure, a Key mediator of bodies response to Gram negative septicaemia. High concentrations of TNF induce shock-like symptoms
- Exerts an interferon-like effect against viruses
- Enhanced HLA class I expression
- Anti-tumour effect (e.g. phospholipase activation)
- TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis.
 It also cause activation of NFkB
- Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins
- Promotes the proliferation of fibroblasts and their production of protease and collagenase.
- the prolonged exposure to **low concentrations of TNF can result in cachexia**, a wasting syndrome. This can be found, for example, in cancer patients.
- Raised levels lead to increased insulin resistance

TNF blockers

- Used to treat IBD, rheumatoid arthritis, ankylosing spondylitis and psoriasis.
- Examples
 - ⇒ **Infliximab:** monoclonal antibody, IV administration
 - ⇒ **Etanercept:** fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors, subcutaneous administration
 - ⇒ **Adalimumab:** monoclonal antibody, subcutaneous administration
- Adverse effects of TNF blockers
 - ⇒ reactivation of latent tuberculosis.

- Contraindications of usage of TNF- alpha antagonist
 - ⇒ Active infection
 - ⇒ Active TB
 - ⇒ MS (Multiple sclerosis)
 - ⇒ Heart failure (NYHA grade 3-4).
 - ⇒ Pregnancy and Breast feeding

Nitric oxide (NO)

Nitric oxide (NO)

- Has a half-life of only a few seconds.
- ⇒ It is not stored by the body but is synthesized as a result of activation.
- **○** Nitrate drugs stimulate the formation and release of NO.
- Relaxation of smooth muscle cells in vessel walls leads to the dilation of coronary arteries, pulmonary arteries, and peripheral veins.
- Peripheral vasodilation leads to a decrease in cardiac preload.

Overview

- It is formed from L-arginine and oxygen by nitric oxide synthetase (NOS).
- An inducible form of NOS has been shown to be present in macrophages.
- · Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals
- Nitric oxide generates cyclic quanosine monophosphate (cGMP) as the second messenger
- Can freely diffuse across cell membranes, so NO can act as an intracellular and extracellular signaling molecule

Effects

- Acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing Ca2+ levels
- Causes smooth muscle relaxation and subsequent dilation of blood vessels
- Inhibits platelet aggregation

Clinical relevance

- Underproduction of NO is implicated in hypertrophic pyloric stenosis
- · Lack of NO is thought to promote atherosclerosis
- In sepsis increased levels of NO contribute to septic shock
- Organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure)
- Sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions
- N2O, also known as 'laughing gas', is often used in obstetrics and trauma for pain relief

Endothelin-1 (ET-1)

- A 21-amino-acid polypeptide
- Endothelin-1 is a potent vasoconstrictor that is encoded by the EDN1 gene and produced by vascular endothelial cells.
- It is a highly potent vasoconstrictor and plays a part in the modulation of vascular tone
- It may have a role in diseases such as Raynaud's phenomenon
- Its levels increase when the endothelium is stressed, for example in trauma or oxidative stress
- Clinical significance
 - ⇒ Long term ET-1 exposure has been associated with hypertrophic cardiomyopathy.
 - ⇒ Endothelin-1 receptor antagonists (Bosentan) are used in the treatment of pulmonary hypertension. Inhibition of these receptors prevents pulmonary vasculature constriction and thus decreases pulmonary vascular resistance.

Kinins

Overview

- Kinins are mostly produced at inflamed or injured tissue of the body
- kinins are potent vasoactive basic peptides involved in the inflammatory response
- Their activation leads to release of chemotactic cytokines

Functions

- increase vascular permeability
- cause vasodilation, pain, and the contraction of smooth muscle
- stimulate arachidonic acid metabolism

Erythrocyte sedimentation rate (ESR)

Overview

 The ESR is a non-specific marker of inflammation and depends on both the size, shape and number of red blood cells and the concentration of plasma proteins such as fibrinogen, alpha2-globulins and gamma globulins

Causes of a high ESR

- · temporal arteritis
- myeloma
- other connective tissue disorders e.g. systemic lupus erythematosus
- other malignancies
- infection
- other factors which raise ESR: increasing age, female sex, anaemia

Causes of a low ESR

- polycythaemia
- · afibrinogenaemia/ hypofibrinogenaemia

Leukocyte alkaline phosphatase

Raised in	Low in
 Myelofibrosis Leukemoid reactions Polycythemia rubra vera Infections Steroids, Cushing's syndrome Pregnancy, oral contraceptive pill 	 Chronic myeloid leukemia Pernicious anemia Paroxysmal nocturnal hemoglobinuria Infectious mononucleosis

Thymus

T cells = Thymus

B cells = Bone marrow

The Thymus arises from the Third pharyngeal pouch

Embryology: Thymus epithelium arises from the 3rd pharyngeal pouch (endoderm).

Function: Maturation and differentiation of T lymphocytes

Location: The thymus is a gland composed of two identical lobes, located in the superior anterior superior mediastinum, in front of the heart and behind the sternum.

Clinical significance

- Thymic hypoplasia or aplasia: DiGeorge syndrome, SCID
- Thymoma: tumor of thymic epithelial cells: Seen in myasthenia gravis, pure red cell aplasia, immunodeficiency with thymoma

Thymic cortex and medulla

- The <u>cortex</u> is the area of the thymus that is dense and full of immature T cells.
- The medulla is the area of the Thymus that is pale and full of mature T cells

B cells (B lymphocytes)

Origin: Originate and mature in the bone marrow

Function

- Major component of the adaptive immune system: The humoral immune response of the adaptive immune system mainly consists of B cells and antibodies.
- After activation, B cells differentiate into plasma cells that produce and secrete antibodies

Surface proteins

- B cells express numerous proteins on their surface:
 - ⇒ CD19, CD20 , CD21 (used by EBV), and CD40
 - ⇒ MHC II
 - ⇒ IqG
 - ⇒ B7

Plasma cells

- Plasma cells are fully differentiated cells from B-cells and hence lack these features (i.e. they lack surface-bound IgG and MHC class II and cannot undergo somatic hypermutation or isotype switching).
- plasma cells do not have surface-bound IgG (unlike B-cells).
- plasma cells cannot undergo somatic hypermutation (unlike B-cells).
- plasma cells cannot undergo isotype switching (unlike B-cells).

B lymphocytes **VS** T lymphocytes

	B lymphocytes	T lymphocytes
Site of production	bone marrow. germinal centre of lymph nodes and spleen.	produced in the bone marrow but mature in the thymus Paracortical region of lymph nodes and spleen.
Functions	Humoral immunity	Cell-mediated immunity; ⇒ protection against intracellular organisms, protozoa and fungi; ⇒ graft rejection; ⇒ control of neoplasms.
% of total lymphocytes:	⇒ 12%⇒ mainly fixed.	 70-80% (the majority of circulating lymphocytes in plasma). mainly circulating; long-lived memory cells.

T cells (T lymphocytes)

Origin

• Originate from lymphoid progenitor cells in the bone marrow and mature in the thymus.

Distribution

- T lymphocytes compose the majority of circulating lymphocytes in plasma.
- Lymph nodes:
 - The paracortical areas contain T cells and accessory cells.
 - B cells are found within the cortex in follicles, which have central areas known as germinal centres.
 - The medulla contains large blood vessels and sinuses, and medullary cords that contain plasma cells secreting antibody.

Function

- A major component of the adaptive immune response
- Essential for cell-mediated immunity
 - ⇒ T lymphocytes are involved in cell-mediated acquired immune responses, whereas B lymphocytes are involved in humoral immunity and produce immunoglobulins.

Mechanism of action

- T cells recognise antigen only when presented by (self) MHC molecules on an antigen
 presenting cell (Co-operation with other cell types is required for T cell recognition of
 antigen)
- Patients with HIV have a deficiency of T-cells (CD4 T-cell lymphocytes)

T cell subtypes

 T cells are largely divided into cytotoxic T cells (CD8+), T helper cells (CD4+), and regulatory T cells.

What is the predominant site in the lymph node that contains T cells?

Paracortex

CD8 proteins on the surface of cytotoxic T cells interact with MHC I receptors, while CD4 proteins on the surface of T-helper cells interact with MHC II receptors.

Rule of 8:

- \bigcirc MHC I x CD 8 = 8.
- \bigcirc MHC II x CD 4 = 8.

T-Helper cells (CD4+)

- · Activated via antigen presentation by MHC class II receptors
- There are two major subsets of T-Helper cells:
 - → Th1
 - involved in the cell mediated response and delayed (type IV) hypersensitivity
 - Immune response to intracellular pathogens (viruses, intracellular bacteria)
 - secrete IFN-gamma, IL-2, IL-3
 - ⇒ Th2
 - involved in mediating humoral (antibody) immunity e.g. stimulating production of IgE in asthma
 - Immune response to extracellular pathogens (bacteria, parasites)
 - secrete IL-4, IL-5, IL-6, IL-10, IL-13
- An increase in the Th1:Th2 ratio is associated with a reduction in the risk of allergic/hypersensitivity reactions.

MRCP-part-1-Jan- 2018 exam: What is most commonly secreted agent by T-helper cells subset 2 (Th2 cells) ?

○ Interleukin 4

Primary immunodeficiency

Disorders may be classified according to which component of the immune system they affect.

Neutrophil disorders

Neurophii disorders		
Disorder	Underlying defect	Notes
Chronic granulomatous disease	Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species	Caused by a failure of intracellular killing (no respiratory burst). Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. Staphylococcus aureus and fungi (e.g. Aspergillus) Negative nitroblue-tetrazolium test Screening is by the nitroblue tetrazolium (NBT) test Abnormal dihydrorhodamine flow cytometry test
Chediak- Higashi syndrome	Microtubule polymerization defect which leads to a decrease in phagocytosis	Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen Giant granules in neutrophils and platelets
Leukocyte adhesion deficiency	Defect of LFA-1 integrin (CD18) protein on neutrophils	Recurrent bacterial infections. Delay in umbilical cord sloughing may be seen Absence of neutrophils/pus at sites of infection

B-cell disorders

Disorder	Underlying defect	Notes
Common variable immunodeficiency CVID	Many varying causes	Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphona
Bruton's (x-linked) congenital agammaglobulinaemia	Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development	X-linked recessive. Recurrent bacterial infections are seen Absence of B-cells with reduce immunoglogulins of all classes
Selective immunoglobulin A deficiency	Maturation defect in B cells	Most common primary antibody deficiency. Recurrent sinus and respiratory infections Associated with coeliac disease and may cause false negative coeliac antibody screen

T-cell disorders

Disorder	Underlying defect	Notes
DiGeorge syndrome	22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches	Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate

Combined B- and T-cell disorders

Combined B- and T-cell disorders: SCID WAS ataxic (SCID, Wiskott-Aldrich syndrome, ataxic telangiectasia)

Disorder	Underlying defect	Notes
Severe combined immunodeficiency	Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency	Recurrent infections due to viruses, bacteria and fungi. Reduced T-cell receptor excision circles Stem cell transplantation may be successful
Ataxia telangiectasia	Defect in DNA repair enzymes	Autosomal recessive. Features include: 1. cerebellar ataxia, 2. telangiectasia (spider angiomas), 3. recurrent chest infections 4. and 10% risk of developing malignancy, lymphoma or leukaemia
Wiskott-Aldrich syndrome	Defect in WAS gene	X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia. Low IgM levels Increased risk of autoimmune disorders and malignancy

Selective IgA deficiency

The history of mucosal infections (sinus and gastrointestinal) and the family history of immune cytopenia and coeliac disease are suggestive of selective IgA deficiency.

Definition

 Most common primary immunodeficiency that is characterized by a near or total absence of serum and secretory IgA

Features

- Often asymptomatic
- Recurrent infections
 - ⇒ May manifest with sinusitis or respiratory infections (S. pneumoniae, H. influenzae)
 - Chronic diarrhea, partially due to elevated susceptibility to parasitic infection (e.g. by Giardia lamblia)
- Associated with autoimmune diseases (e.g., gluten-sensitive enteropathy, inflammatory bowel disease, immune thrombocytopenia) and atopy
 - ⇒ 10-fold increased risk of coeliac disease
 - ⇒ Pernicious anaemia and hence gastric carcinoma
 - ⇒ ↑ Adverse reactions to blood products
 - Patients with selective IgA deficiency should be tested for the presence of anti-IgA antibodies prior to transfusion with blood products.
- Anaphylactic reaction to products containing IgA (e.g., intravenous immunoglobulin)
- Associated with IgG2 deficiency
 - ⇒ They are more likely than the general population to have an IgG2 deficiency, leading to recurrent bacterial infections
 - ⇒ The possibility of IgG2 deficiency should always be investigated in IgAdeficient individuals with a history of recurrent bacterial infections, but
 Staphylococcus aureus is the exception

The Six A's of selective IgA deficiency: Asymptomatic, Airway infections, Anaphylaxis to IgA-containing products, Autoimmune diseases, Atopy

Diagnosis

- low serum IgA level, with normal IgG and IgM levels
- False-positive pregnancy tests

Treatment

- No specific treatment
- Prophylactic antibiotics
- Intravenous infusion of IgA is not recommended because of the risk of anaphylactic reactions (caused by the production of anti-IgA antibodies).

To prevent transfusion reactions, IgA-deficient patients must be given washed blood products without IgA or obtain blood from an IgA-deficient donor.

IgG subclass deficiency

Overview

 A decrease of one of IgG subclass (IgG1, IgG2, IgG3 or IgG4) in a patient whose total IgG concentration is normal.

IgG1 deficiency

 Almost always presents as hypogammaglobulinemia, since IgG1 normally makes up about 70 percent of total IgG. Therefore, only those patients with IgG1 deficiency with normal total IgG should be diagnosed with selective IgG1 deficiency.

IgG2 deficiency

- More common in children
- Infections with Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis are characteristic, since IgG2 comprises most of the antibody response against

polysaccharide capsular antigens \rightarrow multiple presentations with otitis media and respiratory tract infections.

• If these patients are vaccinated with Pneumovax, they are still unable to mount a response to S. pneumoniae antigens

laG3 deficiency

- More common in adults.
- Infections with Moraxella catarrhalis and S. pyogenes are typical → frequent chronic sinusitis

IgG4 deficiency

May or may not be associated with symptomatic sinopulmonary infections.

Isolated IgD deficiency

- IgD are surface receptors of B lymphocytes
- No specific signs or symptoms
- increased viral respiratory tract infections.
 - ⇒ IgE deficiency leads to both viral and parasitic infections
- IgA, IgG and IgM levels are entirely normal
- Isolated IgD deficiency has been identified amongst people of Basque origin, hence the link to northern Spain
- Not require any specific treatment

Common variable immunodeficiency (CVID)

Definition

 primary immunodeficiency with low serum levels of all immunoglobulins despite phenotypically normal B cells

Epidemiology

- The most common clinically significant primary immunodeficiency is CVID.
 - ⇒ IgA deficiency is more common, but most are asymptomatic.
- Sex: ♀ = ♂
- Onset: present later than other B cell defects (usually 20–35 years of age)

Pathophysiology

- Most cases are sporadic with no known family history (No clear pattern of inheritance)
- B cells are phenotypically normal but are unable to differentiate into Iq-producing cells, (Bcell dysfunction) resulting in low immunoglobulins of all classes.

Features

- Recurrent pyogenic respiratory infections, e.g., sinopulmonary infections (in rare cases, enteroviral meningitis)
- Associated with a high risk of lymphoma, gastric cancer, bronchiectasis, and autoimmune disorders (e.g., rheumatoid arthritis, autoimmune hemolytic anemia, immune thrombocytopenia, vitiligo)

Investigations

- Quantitative immunoglobulin levels: low levels of lqG, lqA, and lqM
- Decreased number of plasma cells
- Flow cytometry shows subsets of normal B and T cells
- Poor response to immunizations

Treatment

- Intravenous immunoglobulin (IVIG) replacement therapy (first line), the best option to prevent recurrent chest infections.
- Prophylactic antibiotics
- ⊃ CVID →B-cell Cannot differentiate into plasma cells → low immunoglobulins but normal or decreased B cells.
- ⇒ Bruton's → Pre-B lymphocytes are increased because there's a maturation defect.

MRCP-part-1-May-2018

H/O recurrent Giardia lamblia diarrhea and multiple upper respiratory infections since birth. serum analysis reveals normal levels of mature B lymphocytes. What other finding on serum analysis predisposes the patient to recurrent diarrheal infections?

- **⊃** Deficiency in IgA
 - The patient has common variable immunodeficiency disorder (CVID)
 - IgA prevent the binding of pathogens to the epithelial cells; thus, preventing protozoa like Giardia lamblia from causing inflammation. Its absence, therefore, leads to the increased likelihood of repeat infection of the GI mucosa

<u>Bruton's agammaglobulinemia (X-linked agammaglobulinemia)</u>

Live vaccines (e.g., MMR) are contraindicated in patients with Bruton agammaglobulinemia.

Pathophysiology

- X-linked recessive disease caused by a mutations in the gene coding for Bruton tyrosine kinase (BTK) leads to complete deficiency of B lymphocytes
- The most common genetic event is a **missense mutation** (substitution in one amino acid in a protein).

Epidemiology: occurs mainly in boys

Features

- Symptoms develop between 3 and 6 months of age when maternal IgG levels in fetal serum start to decrease.
- Hypoplasia of lymphoid tissue (e.g., tonsils, lymph nodes)
- Recurrent, severe, pyogenic infections (e.g., pneumonia, otitis media), especially with encapsulated bacteria (S. pneumoniae, N. meningitidis, and H. influenzae)
- Hepatitis virus and enterovirus (e.g., Coxsackie virus) infections

Diagnosis

- Flow cytometry
 - ⇒ Absent or low levels of B cells (marked by CD19, CD20, and CD21)
 - ⇒ Normal or high T cells
- Low immunoglobulins of all classes
- · Absent lymphoid tissue, i.e., no germinal centers and primary follicles

Treatment

- IV immunoglobulins
- Prophylactic antibiotics

Severe combined immunodeficiency disease (SCID)

SCID is due to either a deficiency in IL-2R gamma chain (most common, X-linked) or deficiency in adenosine deaminase (autosomal recessive)

Overview

- Numerous genetic mutations → Combined B- and T-cell disorder → immunodeficiency
- X-linked recessive mutations → defective IL-2R gamma chain receptor linked to JAK3 (most common SCID mutation)
- Autosomal recessive → Adenosine deaminase deficiency (it aid in breakdown of deoxyadenosine, which is a breakdown product of DNA) → Accumulation of toxic metabolites (deoxyadenosine and dATP) (Deoxyadenosine is toxic to lymphocytes, thus accumulation of this leads to apoptosis of lymphocytes)

Features (usually manifests in the first year of life)

- Recurrent infections
- Diarrhea
- Dermatitis
- · Failure to thrive
- Lymph nodes and tonsils may be absent

Diagnosis

- Flow cytometry: absent T cells , abnormal function of B-cells
- · CXR: absent thymic shadow
- Lymph node biopsy: absent germinal centers
- ↓ Lymphocyte count (< 3000/µL)

Treatment

Bone marrow transplantation (the best initial curative treatment)

Prognosis

Without intervention, SCID usually results in severe infection and death in children by age 2
years.

DiGeorge syndrome

DiGeorge syndrome - a T-cell disorder

Definition

 A syndrome characterized by defective development of the third and fourth pharyngeal pouches leading to hypoplastic thymus and parathyroids

Pathophysiology

- Autosomal dominant; microdeletion at chromosome 22 → Abnormal development of the third and fourth pharyngeal pouches → thymic aplasia and defective parathyroid → T-cell deficiency and dysfunction → primary immunodeficiency
 - ⇒ The thymus arises from the 3rdpharyngeal pouch,
 - ⇒ the parathyroid glands receive contribution from both 3rd and 4th pouches.
- It is an example of a microdeletion syndrome.

Features

- Thymus aplasia/hypoplasia → Recurrent infections (viral/fungal/PCP pneumonia) due to T-cell deficiency
- Parathyroid gland hypoplasia → hypocalcaemic tetany

- Cardiac anomalies: (e.g., tetralogy of Fallot, VSD, ASD)
- · Facial abnormalities:
 - ⇒ Cleft palate
 - ⇒ Micrognathia (small lower jaw) and/or retrognathia
 - □ Dysplastic ears
 - ⇒ High and broad nasal bridge

Investigations

- Chest X-ray shows absence of the thymic shadow.
- Low levels of serum calcium (Ca2+) and parathormone (PTH)
- J Absolute T-lymphocyte count
- · Delayed hypersensitivity skin testing
- Fluorescence in situ hybridization (FISH) → Detection of 22q11.2 deletion

MRCP-part-1- May 2019 exam: In a patient having DiGeorge syndrome, which infection is he most at risk from, secondary to his immune system dysfunction? *Cryptococcus* neoformans (T-cell dysfunction → ↑↑ risk from recurrent viral and fungal infections)

Wiskott-Aldrich syndrome (WAS)

Wiskott-Aldrich syndrome: Classic tetrad of:

- 1. Purpura (bleeding diathesis)
- 2. Eczema (high risk of atopic disorders)
- 3. Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)
- 4. ↑ Risk of autoimmune diseases and hematological malignancies

Definition

 Wiskott-Aldrich syndrome (WAS) is defined as an X-linked hereditary disorder associated with adaptive and innate immunodeficiency, micro-thrombocytopenia, eczema, and an increased risk of autoimmune disorders and malignancy.

Pathophysiology

"Loss-of-function" mutation in WASP gene (X-linked recessive inheritance) → combined
 B- and T-cell dysfunction and thrombocytopenia

Epidemiology: occurs primarily in males

Features

- Classic tetrad
 - 1. Purpura (bleeding diathesis)
 - 2. Eczema (high risk of atopic disorders)
 - 3. Recurrent bacterial, viral, and fungal infections (e.g., chest, otitis media)
 - Increased risk of autoimmune diseases and hematological malignancies (e.g., lymphoma, leukemia)

Investigations

- Thrombocytopenia with small platelets
- Low IgM and IgG levels
- ↑ IgE and IgA
- Genetic analysis (confirmatory test): mutated WASp gene

Prognosis

• The disease has variable penetrance, which means that life expectancy can range from 6 - 30 years.

Complement deficiencies

- C3 deficiency is associated with recurrent bacterial infections,
- C5 deficiency is more characteristically associated with disseminated meningococcal infection
- ⊃ Deficiencies of the classical complement pathway such as C1 and C4 deficiencies are strongly associated with the development of systemic lupus erythematosus;
- → deficiencies of the alternative pathway, such as C3 and C5-9, are associated with increased risk of recurrent pyogenic infections.

Overview

- Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body.
- Complement proteins are involved in chemotaxis, cell lysis and opsonisation.
- Most of complement deficiencies are inherited in autosomal recessive fashion; the
 exception being properdin deficiency, which is usually described as having an X-linked
 inheritance pattern.

C1 inhibitor (C1-INH) protein deficiency

- · causes hereditary angioedema
- · C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)

- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura, vasculitidies
- mechanism
 - ⇒ complement activity is associated with clearance of circulating immune complexes
 - ⇒ If immune complexes are not cleared, they undergo → tissue deposition where an inflammatory process is triggered, leading to SLE

C3 deficiency

- causes recurrent bacterial infections
- Deficiencies of C3 is more commonly associated with haemolytic uraemic syndrome

C5 deficiency

- predisposes to Leiner disease
- · recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency

- encodes the membrane attack complex (MAC)
- particularly prone to Neisseria meningitidis infection
- Absent classical and alternate pathway activity

Membrane attack complex (MAC)

- Formed by C5b, C6, C7, C8, and multiple copies of C9 complement proteins on pathogen cell membranes
- Function → lyses pathogens
- Inhibited by CD59
 - ⇒ This exists on body cells to protect them from MAC.

⇒ paroxysmal nocturnal haemoglobinuria, results in red cells that lack CD59. These red cells can, therefore, be lysed by MAC.

Decay-accelerating factor (DAF) deficiency is associated with → Paroxysmal nocturnal haemoglobinuria (PNH).

Diagnosis

CH50 assay screening test

MRCPI-part-1-jan-2017: Post splenectomy what type of immunodeficiency is occurs?

Humoral

Post splenectomy there is increased susceptibility to H. Influenzae, N.
 Meningitidis and Strep pneumonia which are encapsulated organisms due to the loss of splenic macrophages which are part of the humoral response.

MRCPUK-pat-1-May 2019 exam: A 23-year-old man is admitted with sepsis. Blood cultures are reported as *Neisseria gonorrhoeae*. Which complement protein is the patient most likely to deficient in?

• C5-9

Hereditary angioedema

Hereditary angioedema - C1-INH deficiency

Hereditary angioedema - C4 is the best screening test inbetween attacks

Overview

- Hereditary angioedema is an <u>autosomal dominant</u> condition associated with <u>low plasma</u> <u>levels of the C1 inhibitor (C1-INH) protein</u>.
- C1-INH is a multifunctional serine protease inhibitor

Pathophysiology

- Deficiency of C1 esterase inhibitor leads to persistent activation of the classical complement pathway and C4 levels are frequently low secondary to activation and consumption.
 - ⇒ ↓C1 inhibitor allow C1 to act on C4 and C2
- Mechanism of attacks: uncontrolled release of <u>bradykinin</u> resulting in oedema of tissues.

Investigation

- C1-INH level is low during an attack
- Low C2 and C4 levels are seen, even between attacks.
- Serum C4 is the most reliable and widely used screening tool
- Angioedema does not readily cause a rise in mast cell tryptase.

Features

- Painless, non-pruritic swelling of subcutaneous/submucosal tissues
 - ⇒ urticaria is not usually a feature
 - ⇒ attacks may be proceeded by painful macular rash
- May affect upper airways, skin, genital or abdominal organs (can occasionally present as abdominal pain and vomiting due to visceral oedema)
- Triggers include stress, infection and menstruation

Management

- Acute: IV C1-inhibitor concentrate (1000-1500 units given intravenously over 20-30 min),
 - ⇒ fresh frozen plasma (FFP) if this is not available
- Prophylaxis:
 - ⇒ Anabolic steroid, synthetic androgen: <u>Danazol</u> may help
 - ⇒ Aminocaproic acid

Complication

• If treatment fails to normalise the C4 levels and they remain persistently low, these patients are at an <u>increased risk of developing SLE</u>.

Other Causes of angioedema

- Bradykinin-mediated angioedema
 - ⇒ Hereditary angioedema (inherited C1 inhibitor deficiency)
 - ⇒ Acquired angioedema (acquired C1 inhibitor deficiency)
 - Often associated with lymphoproliferative diseases and B-cell malignancies
 - ⇒ ACE inhibitor-induced (rarely ARB-induced): impaired bradykinin breakdown
 - Can occur within days to 2 years after starting ACE inhibitor
- Histamine-mediated angioedema (mast cell-mediated angioedema)
 - ⇒ Usually coexist with urticaria
 - ⇒ Salicylate- and/or aspirin-associated angioedema
 - ⇒ Moxonidine is a centrally acting antihypertensive and is associated with angioedema
- Idiopathic angioedema: Possible triggers: cold, heat, stress, and exercise

Granulomatous inflammation

Definition

- A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg ,TB), immune-mediated diseases, and foreign bodies.
- A granuloma is a collection of macrophages: giant cells as a nidus of chronic inflammation **Mechanism**
 - Macrophages →↑cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells

Types of granuloma and causes

- Caseating granulomas
 - ⇒ Granulomas with central necrosis
 - ⇒ Found in infections e.g., tuberculosis, fungal infections, tertiary syphilis, Bartonella henselae (cat scratch disease)
- Noncaseating granulomatous inflammation
 - ⇒ Granulomas without central necrosis
 - ⇒ Found in immune-mediated diseases (e.g., sarcoidosis, Crohn disease), sarcoidosis, vasculitis, and foreign body exposure

TNF-α is important for maintaining the granuloma. It is essential to test patients for latent TB before initiating anti-TNF therapy because the drug causes breakdown of the granuloma and can result in disseminated TB.

Third edition

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

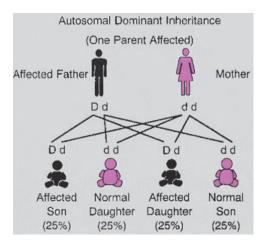
Basic sciences Genetics

Updated

Autosomal dominant conditions

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive



The following conditions are autosomal dominant:

- Achondroplasia
- Acute intermittent porphyria
- Adult polycystic disease
- Antithrombin III deficiency
- Ehlers-Danlos syndrome
- Familial adenomatous polyposis
- · Hereditary haemorrhagic telangiectasia
- Hereditary spherocytosis
- Hereditary non-polyposis colorectal carcinoma
- Huntington's disease
- · Hyperlipidaemia type II
- Hypokalaemic periodic paralysis

- Malignant hyperthermia
- · Marfan's syndromes
- Myotonic dystrophy
- Neurofibromatosis
- Noonan syndrome
- · Osteogenesis imperfecta
- Peutz-Jeghers syndrome
- Retinoblastoma
- Romano-Ward syndrome
- Tuberose sclerosis
- Von Hippel-Lindau syndrome
- Von Willebrand's disease*

As an autosomal dominant condition, two affected parents can expect:

- 1 in 4 chance of an unaffected child
- 1 in 2 chance of an affected heterozygous child
- 1 in 4 chance of an affected homozygous child.

Which disease demonstrates autosomal co-dominant inheritance?

→ Alpha-1-antitrypsin deficiency

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

Achondroplasia

Aetiology

- Mutation in fibroblast growth factor receptor 3 gene (FGFR3) → reduced endochondral ossification
 - ⇒ activation of fibroblast growth factor receptor 3 on chromosome <u>4</u>, resulting in inhibited chondrocyte proliferation.
- · autosomal dominant
- The homozygous form is usually fatal.

Epidemiology

Most common type of skeletal dysplasia and disproportionate short stature (1:40,000 children worldwide affected)

Risk factor

The incidence increases with paternal age.

Pathophysiology

- · Epiphyseal growth cartilage fails,
- there is normal bone formation and repair.
 - ⇒ Therefore, **NO** increased risk of fracture.

Features

becomes obvious within the first year with disparity between a large skull, normal trunk length and short limbs.

- short stature
- short limbs (rhizomelia) with shortened fingers (brachydactyly)
 - ⇒ The fingertips may only come down to the iliac crest, and the shortness of the limbs is often most marked proximally.
 - ⇒ short stature due to shortening of the limbs, but spinal length is maintained.
 - ⇒ The limbs appear broad with deep creases.
- large head (Macrocephaly) with frontal bossing
- midface hypoplasia with a flattened nasal bridge
- · 'trident' hands
- lumbar lordosis
- Normal intelligence

Complications

- Small foramen magnum → compression of the cervical medulla
- Spinal canal stenosis and radiculopathy (of the lower back)
 - ⇒ low back and leg pain,
 - ⇒ paresthesias, dysesthesia,
 - ⇒ incontinence
- Secondary scoliosis
- Recurrent otitis media
- Cardiopulmonary complications (due to a small chest wall)

Diagnostics

- X-ray
 - ⇒ It may be diagnosed radiographically at birth,
 - □ Lateral skull
 - midface hypoplasia,
 - frontal prominence
 - ⇒ pelvis

- narrow in anteroposterior diameter with deep sacroiliac notches and short iliac wings.
- ⇒ Spine
 - progressive narrowing of the interpedicular distance from top to bottom (reverse of normal).
 - ❖ abnormally narrow interpedicular distance → spinal canal stenosis; scoliosis
- ⇒ Extremities
 - bones are short and broad;
 - short fingers
 - metaphyseal irregularity,
 - flaring in the long bones,
 - late-appearing irregular epiphyses.

Management

- medical
 - ⇒ Early administration of **growth hormone** (1–6 years)
- Surgical corrections:
 - ⇒ spinal stenosis, secondary scoliosis, genu varum, foramen magnum decompression

Osteogenesis imperfecta ("brittle bone disease")

Pathophysiology

Autosomal dominant mutation in COL1A1 or COL1A2 genes → ↓ synthesis of normal type I collagen → impaired bone matrix formation (osteogenesis)

Features

- Growth retardation
- Skeletal deformities, brittle bones, and recurrent fractures from minimal trauma
- Blue sclerae due to visible choroidal pigment.
- Progressive hearing loss secondary to otosclerosis
- Brittle, opalescent teeth (dental imperfections) due to a lack of dentin formation.

Types

- type 1:The most common, and milder form.
- Type II: most severe form; lethal perinatally or within the first year

Diagnostics

- DNA test
- Ultrasonography before birth and radiographic skeletal survey afterwards (fractures, callus, deformities)
- Bone or skin biopsy → type 1 collagen mutation

Therapy

- No cure available
- Bisphosphonates; decrease the risk of fractures
- Surgery for functional improvement

Individuals with osteogenesis imperfecta can't BITE: Bones (recurrent fractures), I ("eye" = blue sclerae), Teeth (dental abnormalities), Ears (hearing loss).

MRCPUK-part-1-May-2009 exam: A pregnant woman is known to have polycystic kidney disease. What is the chance her child will also have the disease?

→ 50% (Polycystic kidney disease is usually inherited in an autosomal dominant fashion and hence 50% of her children will be affected, regardless of gender)

Down's syndrome (trisomy 21)

Epidemiology and genetics

• the most common autosomal abnormality

Risk of Down's syndrome with increasing maternal age

Age (years)	Risk
20	1 in 1,500
30	1 in 800
35	1 in 270
40	1 in 100
45	1 in 50 or greater

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age

Cytogenetics

Mode	% of cases	Risk of recurrence
Non-disjunction	94%	1 in 100 if under mother < 35 years
Robertsonian translocation (usually onto 14)	5%	10-15% if mother is translocation carrier 2.5% if father is translocation carrier
Mosaicism	1%	

- The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother
 is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much
 higher.
- Down syndrome have one of the two karyotypes:
 - **1.** 47,XX,+21 (trisomy 21): more common
 - **2.** 46,XY,der(14;21): characterized by the presence of two normal chromosomes 21, one normal chromosome 14 and a product of Robertsonian translocation between chromosomes 14 and 21 (der(14;21); der stands for derivative).

The general risk of trisomy 21 increases with maternal age. This does not, however, apply to translocation trisomies

Features

- face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small ears, round/flat face
- flat occiput
- single palmar crease, pronounced 'sandal gap' between big and first toe
- hypotonia
- congenital heart defects (40-50%, see below)
- duodenal atresia can be diagnosed by U/S at gestation → double bubble sign
- · Hirschsprung's disease

Associations

- ↑↑ risk for developing acute myeloid leukemia (AML) (approximately 1-2% of children with Down syndrome develop AML, the great majority < 5 y) rather than acute lymphoblastic leukemia (ALL), which is a more common form of leukemia in children.
- Other haematological disorders associated with Down's syndrome include:
 - ⇒ Fanconi's anaemia.
 - ⇒ Patients with learning disabilities may be prone to lead poisoning due to pica.

Cardiac complications

- 50% of children with Down's syndrome have a cardiac defect.
- multiple cardiac problems may be present
- endocardial cushion defect (c. 40%, also known as atrioventricular septal canal defects)
- ventricular septal defect (c. 30%)
- secundum atrial septal defect (c. 10%)
- tetralogy of Fallot (c. 5%)
- isolated patent ductus arteriosus (c. 5%)

Later complications

- subfertility:
 - ⇒ Males are almost always infertile due to impaired spermatogenesis.
 - ⇒ Females are usually subfertile, and have an increased incidence of problems with pregnancy and labour
- learning difficulties
- short stature
- repeated respiratory infections (+hearing impairment from glue ear)
- · acute lymphoblastic leukaemia
- hypothyroidism
- Alzheimer's
- atlantoaxial instability

To remember the most important features associated with Down syndrome, think of the 5 A's: Advanced maternal age, duodenal Atresia, Atrioventricular septal defect, AML/ALL, early onset of Alzheimer disease.

Diagnosis

Screening tests (Prenatal)

- Combined test (first trimester) (11–13 weeks)
 - ⇒ Maternal serum
 - ↑ Beta human chorionic gonadotropin (β-hCG)
 - Pregnancy-associated plasma protein A (PAPP-A)

□ Ultrasound

- Nuchal translucency; increases due to the large amount of fluid collecting behind the neck
- Short neck, thickened nuchal fold
- Absent or hypoplastic nasal bone
- Shortened middle phalanges of the fifth digits with clinodactyly
- Shortened long bones (humerus, femur)
- Quadruple test (second trimester) (15–18 weeks)
 - ⇒ ↓ Free estriol
 - ⇒ ↓ Alpha-fetoprotein (AFP)
 - ⇒ ↑ Inhibin A
 - ⇒ ↑ β-hCG

Diagnostic tests (confirmatory test)

- Prenatal → Fetal karyotyping
 - ⇒ Chorionic villus sampling (9–14 weeks)
 - ⇒ Amniocentesis (15–22 weeks)
 - ⇒ Percutaneous umbilical cord sampling (18–22 weeks)
- Postnatal → Chromosome analysis

In the quadruple test, hCG and Inhibin A are both HIgh up (\uparrow) and Estriol and α -fEtoprotein are both dEficient (\downarrow).

Noonan's syndrome

Overview

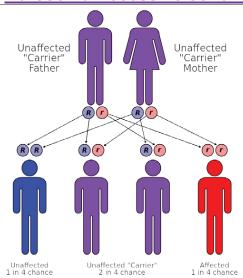
- Relatively common, autosomal-dominant inherited disorder.
- Caused by activating mutations in multiple genes in the Ras/mitogen-activated protein kinase (RAS-MAPK pathway).
- The most commonly implicated gene is PTPN11. on chromosome 12
- · Often thought of as the 'male Turner's',
- In contrast to Turner's syndrome, the karyotype is normal
- The majority of patients lead normal lives

Feature

- features similar to Turner's syndrome:
 - ⇒ short stature,
 - ⇒ webbed neck,
 - ⇒ chest (pectus) deformity
 - widely-spaced nipples,
 - pectus carinatum and excavatum,
- · characteristic features:
 - ⇒ cardiac: (occurs in 50% to 80%)
 - typically, pulmonary valve stenosis
 - atrial septal defect (ASD)
 - occasionally hypertrophic cardiomyopathy
 - ⇒ easy bruising or bleeding (due to coagulation factor deficiency or platelet dysfunction),
 - coagulation problems: factor XI deficiencies
 - ⇒ facial features,
 - triangular-shaped face
 - hypertelorism (increased distance between the eyes)

- downslanting eyes
- vivid blue or blue-green irides
- low-set, posteriorly rotated ears
- ptosis
- ⇒ Boys frequently present with cryptorchidism and manifest delayed puberty.
- ⇒ learning disabilities,
 - Mild cognitive impairment is found in up to 33%
 - Intellectual development may be delayed, but by adulthood intelligence is normal in ⅔ of patients.

Autosomal recessive conditions



- Two copies of the defective gene (one inherited from each parent) are required in order to be born with the disorder.
- Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:
 - some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
 - some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

Autosomal recessive conditions are 'metabolic' - exceptions: inherited ataxias

Autosomal dominant conditions are 'structural' - exceptions: hyperlipidaemia type II,
hypokalaemic periodic paralysis

The following conditions are autosomal recessive:

- Albinism
- · Ataxia telangiectasia
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anaemia
- · Friedreich's ataxia
- Glycogen storage disease

- Haemochromatosis
- Homocystinuria
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Mucopolysaccharidoses: Hurler's
- PKU
- Sickle cell anaemia
- Thalassaemias
- · Wilson's disease

MRCPUK-part-1-May 2012 exam: A man diagnosed as having hereditary hemochromatosis. His wife is not a carrier. What is the chance his child will develop haemochromatosis?

→ 0% (Haemochromatosis is an autosomal recessive condition. If one of the parents has haemochromatosis (i.e. is homozygous) and the other is not a carrier/affected, then all the children will inherit one copy of the gene from the affected parent and hence will be carriers)

Ehlers-Danlos syndrome (EDS)

The classic presentation of EDS involves hyperextensible skin, joint hypermobility, and a tendency to bleed easily.

- Ehlers-Danlos syndrome is a disorder of faulty collagen synthesis most commonly
 affecting collagen type III and V.
- Inheritance patterns and type of collagen affected vary (can be autosomal dominant or recessive)
- Collagen deficiencies in Ehlers-Danlos syndrome are often caused by problems with <u>cross-linking</u>.
- Hypermobile Ehlers-Danlos syndrome (EDS) is the most common of 13 subtypes.
 - ⇒ Most hypermobile people are not aware of the fact and assume that everyone is as flexible as they are.
 - ⇒ Most cases of hypermobile EDS, are inherited in an autosomal dominant manner.
 - ⇒ associated with hypermobile joints, but skin features are much less prominent
 - ⇒ Systemic features may include increased propensity to asthma, mild valve regurgitation and gastrointestinal (GI) symptoms, including constipation and hiatus hernia.
- The most severe form of Ehlers-Danlos syndrome is the vascular type.
 - ⇒ deficiencies in type III collagen.
 - Type III collagen also known as reticulin, and is found primarily in granulation tissue, artery walls, skin, intestines and the uterus.
 - ⇒ involves vascular and organ rupture due to type III collagen deficiency.
- The classical type of Ehlers-Danlos syndrome has deficiencies in type V collagen.
 - ⇒ in which joint and skin manifestations predominate
 - associated with much <u>more severe dermatological features</u>, including hyperelastic skin that splits easily and marked propensity to bruising.
- Kyphoscoliotic EDS is usually inherited in <u>autosomal recessive</u> fashion.

Cardiovascular	 Features of heart valve defects (particularly mitral valve prolapse) Features of aneurysms/dissections of the iliac, splenic, renal arteries, or the aorta Berry/saccular aneurysms of the cerebral arteries → features of subarachnoid hemorrhage
Musculoskeletal	
	 Skeletal abnormalities (e.g., scollosis) features of chronic pain syndrome and marfanoid habitus
Skin	 Tendency to bruise easily Skin hyperextensibility Frequent skin lacerations and poor skin healing (e.g., following surgery)
Other	 Hernias Features of organ rupture (e.g., shock, local pain), especially in vascular EDS



Elbow region of a female patient of Ehlers-Danlos syndrome: The skin of the elbow is hyperelastic (cutis hyperelastica), but rapidly returns to its initial position when released.



Diagnosis

- Definitive diagnosis for <u>all subtypes of EDS</u>, except hypermobile EDS, can be made by molecular genetic testing.
- The genetic basis of hypermobile EDS remains unknown and the diagnosis is made by clinical criteria only.
- A baseline echocardiogram with views of the aortic arch and aorta and regular reevaluations should be obtained to evaluate for <u>mitral valve</u> prolapse and any signs of aortic enlargement.

Prognosis

 Life expectancy is typically normal with the exception of vascular EDS, which has a reduced life expectancy of ~ 50 years.

Pseudoxanthoma elasticum (PXE)

- inherited condition (**usually autosomal recessive***) connective tissue disorder involves the elastic fibres of the **eye**, **skin** and **cardiovascular** system.
 - ⇒ *there are reports of autosomal dominant inheritance in a minority of cases
- caused by mutations in the ABCC6 gene → lack of functional ABCC6 protein leads to
 ectopic mineralization that is most apparent in the elastic tissues of the skin, eyes and
 blood vessels.

- Eve
 - ⇒ retinal angioid streaks
 - due to dystrophic calcification of Bruch's membrane
 - ⇒ Visual loss can occur by infarction of the visual pathways and is likely to explain the chronic changes of optic disc atrophy
- Skin
 - 'plucked chicken skin' appearance small yellow papules on the neck, antecubital fossa and axillae
 - The first clinical sign
- Cardiac
 - ⇒ mitral valve prolapse,
 - ⇒ increased risk of ischaemic heart disease
 - ⇒ Due to loss of elastic tissue, patients have an increased incidence of mitral regurgitation, aortic regurgitation and aortic dissection.

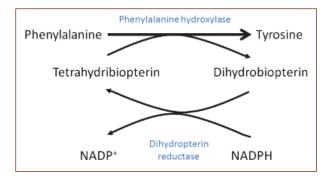
· Gastrointestinal haemorrhage

- CNS
 - ⇒ Cerebral ischaemia in PXE is caused by small vessel occlusive disease.
 - ⇒ Intracranial aneurysms
 - ⇒ Subarachnoid and intracerebral haemorrhages
 - ⇒ Progressive intellectual deterioration
 - ⇒ Mental disturbances, and
 - ⇒ Seizures.

Phenylketonuria (PKU)

Overview

- Autosomal recessive condition
- Caused by a disorder of phenylalanine (an essential amino acid) metabolism.
 - ⇒ usually due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine .
 - ⇒ In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase.
- The gene for phenylalanine hydroxylase is located on chromosome 12.
- The incidence of PKU is around 1 in 10,000 live births.
- High levels of phenylalanine lead to problems such as learning difficulties and seizures.



- The sequence of phenylalanine metabolism is the following: phenylalanine → tyrosine → L-Dopa → dopamine → norepinephrine → epinephrine.
 - the neurological symptoms are most likely caused by a reduction in which neurotransmitters?
 - → Norepinephrine

- usually presents by 6 months e.g. with developmental delay, seizures, typically infantile spasms
- child classically has fair hair and blue eyes
- learning difficulties. Even with dietary treatment some degree of cognitive impairment is seen
- Microcephaly, prominent maxilla, growth retardation and wide-spaced teeth are found in untreated children.

- Eczema
- partial albinism due to decreased tyrosine production.
- 'musty' odour to urine and sweat secondary to phenylacetate, a phenylketone

Diagnosis

- Diagnosis of classic PKU requires raised Phe levels, increased urinary Phe metabolites and normal cofactor (tetrahydrobiopterin) concentrations.
 - plasma levels of tyrosine are difficult to measure, and have diurnal variation. Whilst the levels are often low in patients with PKU, the levels can be normal depending on what time of the day the sample is taken and whether or not the patients are being treated
- Guthrie test: the 'heel-prick' test done at 5-9 days of life also looks for other biochemical disorders such as hypothyroidism
- · hyperphenylalaninaemia
- · phenylpyruvic acid in urine

Management

· Low phenylalanine and high tyrosine diet

Prognosis

 Excellent with normal life expectancy diagnosed early and blood phenylalanine (phe) levels remain within the therapeutic range.

Alkaptonuria

The **black** discoloration of sclera and urine becoming **black** on standing should alert you to the likelihood of **Alkaptonuria**.

Pathophysiology

- Autosomal recessive disorder of phenylalanine and tyrosine metabolism
- Caused by a deficiency of homogentisic acid oxidase responsible for the degradation of homogentisic acid produced from phenylalanine and tyrosine.
- Accumulation of homogentisic acid causes pigmentation of the urine, sclera and connective tissues.
- Alkaptonuria is generally a benign and often asymptomatic condition.

Features

- · Pigmented sclera
- Urine turns black if left exposed to the air
- Deposition in the joints causes cartilage pigmentation (ochronosis) and degeneration.
 - ⇒ Patients develop arthritis at 40 years of age.
 - ⇒ intervertebral disc calcification may result in back pain
 - ⇒ The knees and spine are commonly affected.
 - ⇒ The sacroiliac joint may be spared.
- Renal stones
- Homogentisic acid is a reducing agent, therefore it gives a false <u>positive Glucostix test</u> but normal Clinitest.

Treatment

- · High-dose vitamin C
- Dietary restriction of phenylalanine and tyrosine

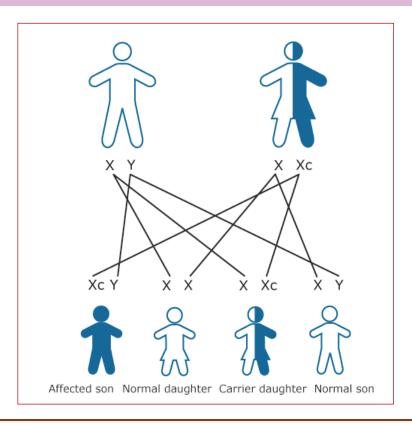
X-linked recessive

X-linked recessive conditions - there is no male-to-male transmission. Affected males can only have unaffected sons and carrier daughters.

X-linked conditions: Duchenne/Becker, haemophilia, G6PD

- The abnormal gene is carried on the X chromosome, and in the carrier female, the normal allele on her other X chromosome protects her from the disease. Since the male does not have this protection, he manifests the disease.
- only males are affected. An exception to this seen in examinations are patients with Turner's syndrome, who are affected due to only having one X chromosome.
- Females only occasionally show mild sign of disease
- X-linked recessive disorders are transmitted by heterozygote females (carriers) and maleto-male transmission is not seen.
- Affected males can only have unaffected sons and carrier daughters.
- heterozygous female carrier →
 - > 50% of male children are affected
 - > 50% of female children are carrier
- The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.
- Many of the inherited eye disorders such as retinitis pigmentosa and ocular albinism are inherited in an x-linked recessive pattern.
 - The following conditions are inherited in a X-linked recessive fashion:
 - ⇒ Androgen insensitivity syndrome
 - ⇒ Becker muscular dystrophy
 - ⇒ Colour blindness
 - ⇒ Duchenne muscular dystrophy
 - ⇒ Fabry's disease
 - ⇒ G6PD deficiency
 - ⇒ Haemophilia A,B

- ⇒ Hunter's disease
- ⇒ Lesch-Nyhan syndrome
- ⇒ Nephrogenic diabetes insipidus
- ⇒ Ocular albinism
- ⇒ Retinitis pigmentosa
- ⇒ Wiskott-Aldrich syndrome
- ⇒ Fragile X syndrome
- The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:
 - ⇔ Chronic granulomatous disease (in > 70%)



What is the most common genetic disorder?

- Sex-linked disorder
 - The most common genetic disorder is actually a relatively minor one, red-green colour blindness, which is seen in 2–4% of men.
 - Other examples of more significant sex-linked disorders include haemophilia A and B.

X-linked dominant disorders

- No carrier (the carrier of a defective gene associated with a disorder, will have the disorder)
- affected woman
 - → Half of the daughters and sons are affected
 - → male will have worse symptoms than female (because women carry two X)
- The gene responsible for a genetic disorder is located on the X chromosome, and only one
 copy of the allele is sufficient to cause the disorder when inherited from a parent who has
 the disorder.
- X linked dominant disorders are rare (for example, vitamin D-resistant rickets).
- They affect both sexes but females more than males.

- Males can only get an X chromosome from their mother whilst females get an X chromosome from both parents. As a result, females tend to show higher prevalence of X-linked dominant disorders because they have more of a chance to inherit a faulty X chromosome.
- Homozygous mother → All children are affected.
- An affected mother with the trait → half the sons and half the daughters inherit the disorder
- when the mother alone is the carrier; she herself will have the disorder.
 - ⇒ 50% Of her daughters and sons will have the disorder.
 - ⇒ 50% will be unaffected.
- Affected females will transmit the condition to 50% of their children, whether male or female.
- When the father alone is the carrier of a defective gene associated with a disorder, he too will have the disorder.
 - ⇒ 100% Of his daughters will have the disorder, since all of his daughters will receive one copy of his single X chromosome.
 - ⇒ none of his sons will have the disorder; sons do not receive an X chromosome from their father.
 - ⇒ affected father → all his daughters are affected but none of his sons.

Vitamin D-resistant rickets

Overview

- Vitamin D-resistant rickets is a X-linked dominant condition
 - ⇒ affected female will transmit the disease to 50% of her sons and 50% of her daughters.
 - ⇒ affected male will transmit the condition to all of his daughters but none of his sons.
- usually presents in infancy with failure to thrive.
- caused by impaired phosphate reabsorption in the renal tubules

Features

- · failure to thrive
- normal serum calcium, low phosphate, elevated alkaline phosphotase
- x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis

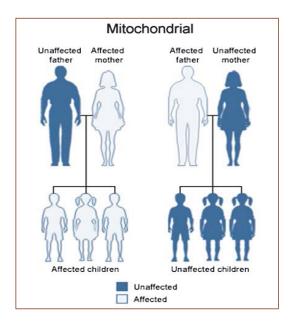
made by demonstrating increased urinary phosphate

Management

- · high-dose vitamin D supplements
- oral phosphate supplements

Mitochondrial diseases

Mitochondrial diseases follow a maternal inheritance pattern



Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is
present in the mitochondria. It encodes protein components of the respiratory chain and
some special types of RNA

Characteristics: Mitochondrial inheritance has the following characteristics:

- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- · all children of affected males will not inherit the disease
- · all children of affected females will inherit it
- · generally, encode rare neurological diseases
- poor genotype: phenotype correlation within a tissue or cell there can be different mitochondrial populations this is known as heteroplasmy)

Histology

 muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples

- Leber's optic atrophy
 - ⇒ Cyanocobalamin (a form of B12) should be avoided as it may lead to blindness in Leber's disease patients.
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
 - ⇒ generalised myoclonus (60%),

- ⇒ epilepsy,
- ⇒ optic atrophy (20%),
- ⇒ short stature (10%),
- ⇒ ataxia.
- ⇒ cognitive decline
- ⇒ encephalopathy (EEG findings of generalised slow waves)
- ⇒ sensorineural hearing loss
- ⇒ impaired glucose tolerance.
- · sensorineural hearing loss

Myoclonic epilepsy with ragged red fibres (MERRF)

A young patient presenting with cognitive impairment developing after a period of normal development, seizures, myoclonic jerks, Wolff-Parkinson White syndrome and worsening vision (consistent with optic atrophy).

Diagnosis \rightarrow (MERRF), which is a mitochondrial DNA disorder diagnosed by \rightarrow ragged red fibres on muscle biopsy.

Kearns-Sayre syndrome

Kearns-Sayre syndrome:

- Mitochondrial inheritance
- Onset < 20-years-old
- Triad of:
 - ⇒ External ophthalmoplegia
 - ⇒ Retinitis pigmentosa and
 - **⇒** Heart block.

Overview

- mitochondrial DNA mutation.
- onset in patients < 20 years old

- external ophthalmoplegia → Ptosis
- · retinitis pigmentosa
- heart conduction defect
- sensorineural hearing loss is almost universal in those who survive into the fourth decade of life; this may not be fully corrected with hearing aids.
- Other associated features:
 - ⇒ cerebellar ataxia,
 - ⇒ raised cerebrospinal fluid (CSF) proteins,
 - ⇒ proximal myopathy.
 - ⇒ short stature
 - multiple endocrinopathies including diabetes mellitus, hypoparathyroidism, and Addison disease.

Diagnosis

- Muscle biopsy may reveal ragged red fibers.
- Muscle histochemistry reveals deficiency of cytochrome c oxidase (mitochondrial respiratory chain enzyme).

Prognosis

Patients rarely live beyond their 40s and there are no therapeutics currently available.

Kallman's syndrome

Kallman's - LH & FSH low - normal

Klinefelter's - LH & FSH - raised

Overview

- Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism.
- It is usually inherited as an X-linked recessive trait.
- Caused by failure of GnRH-secreting neurons to migrate to the hypothalamus → gonadotrophin releasing hormone (GnRH) deficiency
- May arise due to abnormalities of the KAL-1 or KAL-2 gene (encoding anosmin-1 and FGF-1).
- There is isolated gonadotrophic deficiency (may be evidenced by a normal prolactin).
- The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Incidence

- 1 in 10.000 males
- More common in men: male to female ratio of 4:1.

- Hypogonadotrophic hypogonadism
 - ⇒ Sex hormone levels are low
 - ⇒ LH, FSH levels are inappropriately low/normal
 - ⇒ Lack of development of secondary sexual characteristics
 - ⇒ Primary amenorrhoea.
- Infertility
 - ⇒ In male individuals: cryptorchidism and low sperm count
 - ⇒ In female individuals: primary amenorrhea
- Cryptorchidism (Cryptorchidism is more suggestive of Kallman's than Klinefelter's syndrome)
 - Cryptorchidism is the absence of one or both testes from the scrotum (undescended testis).
- Anosmia present in 75% (Lack sense of smell) due to failure of the olfactory bulb to develop, leading to loss of gonadotropin releasing hormones.
- · Patients are typically of normal or above average height
- No mental retardation
- Delayed puberty: (e.g., absent thelarche in female individuals, decreased growth spurt)

- Associated disorders
 - ⇒ Renal agenesis
 - ⇔ Cleft lip/cleft palate
 - ⇒ Visual defects : colour blindness
 - ⇒ Deafness

Diagnosis

- Diagnostic test → Fluorescent in situ hybridisation (FISH) is currently the best means of a genetic diagnosis
- Absent olfactory bulbs are present on 75% of MRI scans in these patients.
 - \Rightarrow The appearance on cerebral MRI \rightarrow Absent olfactory bulbs

Treatment

- For a male who begin a relationship with a woman
 - ➡ Pulsed (NOT Continuous) GnRH treatment is needed to restore LH and FSH release.
 - It needs to be continued for as long as fertility is required.
 - As natural GnRH release is pulsatile, continuous therapy fails to lead to LH and FSH release.
 - Once his family is complete, switching to testosterone therapy may be more convenient for him.
 - Although Testosterone supplementation will restores secondary sexual characteristics, it doesn't restore fertility and is therefore not appropriate here.
 - FSH can be used to induce fertility, but it is less effective than pulsed GnRH therapy.
- If fertility is not required, there is no need to stimulate spermatogenesis with (GnRH) or gonadotropins; only testosterone replacement is required.
- LH can be used in conjunction with FSH to induce fertility in women with Kallmann syndrome.
- For a woman who wants to start a family:
 - ⇒ HCG to drive production of gonadal steroid hormones, FSH to drive ovulation, harvesting of eggs, and IVF. This process is most effective in achieving successful pregnancy.

Klinefelter's syndrome

Klinefelter's? - do a karyotype

Overview

- Klinefelter's syndrome is associated with male phenotype and 47, XXY karyotype
- the commonest form of which is XXY, is the result of chromosomal non-dysjunction; as such, it does not follow a mendelian pattern of inheritance.

- it is the most common chromosomal disorder associated with male hypogonadism and infertility.
- Incidence: between 1 in 500 and 1 in 1000.
- The rate of chromosomal non-dysjunction increases with increasing maternal age and increasing paternal age, each parent contributing 50% of the risk. Around 60% of Klinefelter cases do not survive the fetal period.
- has no specific genetic pattern of inheritance
 - \Rightarrow chances of inheriting the disorder \rightarrow < 1%

Features

- often taller than average
- lack of secondary sexual characteristics
- small, firm testes.
- infertile, azoospermia
- gynaecomastia
 - increased incidence of breast cancer (20 times higher than a normal male).
- elevated gonadotrophin levels (↑↑LH/FSH) due to testicular failure
 - \Rightarrow Leydig cell dysfunction \rightarrow \downarrow testosterone \rightarrow \uparrow LH \rightarrow \uparrow estrogen.
 - \Rightarrow dysgenesis of seminiferous tubules $\Rightarrow \downarrow$ inhibin B $\Rightarrow \uparrow$ FSH.
- Low testosterone levels
- Low HDL cholesterol, elevated triglyceride ,normal or increased (LDL)
- increased cardiovascular risk due to lipid abnormality.
- decrease bone mineral density → increased risk of osteoporotic fractures.

Investigation

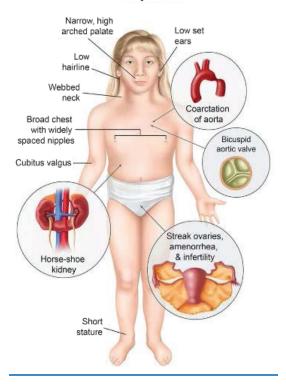
- Diagnosis is by chromosomal analysis
- the most appropriate investigation in suspected cases → FSH, LH
 - ⇒ Both FSH and LH are raised in Klinefelter syndrome, and elevation would be a strong pointer to confirming the underlying diagnosis.
 - ⇒ more useful than Testosterone (wouldn't indicate whether the defect was at the level of the pituitary or the testes)

Treatment → **Testosterone**

Testosterone is known to improve bone mineralization and is the treatment of choice

Turner's syndrome

Turner syndrome



Turner's syndrome - most common cardiac defect is bicuspid aortic valve

Overview

- affects around 1 in 2,500 females.
- caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes.
- · denoted as 45,XO or 45,X

- · short stature
- shield chest, widely spaced nipples
- webbed neck
- cardiac defects:
 - ⇒ bicuspid aortic valve (15%),
 - ⇒ coarctation of the aorta (5-10%)
 - hypertension and systolic murmur

- primary amenorrhoea
- · associated absent uterus and streak ovaries
- cystic hygroma (often diagnosed prenatally)
- · high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- keloid scars
- lymphoedema in neonates (especially feet)
- Horseshoe kidney is strongly associated with Turner's syndrome
 - ⇒ often initially presents with stone disease, pelviureteric junction (PUJ) obstruction, trauma, infections and tumors.
 - ⇒ In a pediatric patient with multiple urinary tract infections or renal stones, imaging must be performed to rule out this congenital anomaly.
 - Which anatomical structures is responsible for horseshoe kidney anomaly during normal embryological development?
 - **▶** Inferior mesenteric artery
 - occurs when the isthmus of the kidney becomes trapped behind the inferior mesenteric artery as the kidneys ascend during embryonic life.

Associated conditions

- · autoimmune diseases:
 - ⇒ autoimmune thyroiditis (hypothyroidism (much more common in Turner's))
 - ⇒ and Crohn's disease
- Hypertension is quite common in Turner syndrome (10%) and is typically idiopathic essential. In a small proportion causes can include:
 - ⇒ coarctation of the aorta
 - ⇒ and renal dysfunction due to horsehoe kidney.
- metabolic abnormalities (dyslipidaemia and glucose intolerance)
- recurrent otitis media.
- Diabetes mellites
 - ⇒ Although the incidence of diabetes mellitus is increased in patients with Turner syndrome, <u>it is thought to be driven by insulin resistance</u> and is <u>very responsive to</u> weight loss.

Diagnosis

• $\underline{\text{karyotype}} \rightarrow \text{identification of 45X0}$.

Prognosis

- What condition is responsible for most of the excess mortality associated with Turner syndrome?
 - ⇒ Thoracic aortic aneurysm rupture

Marfan's syndrome

Marfan's syndrome is caused by a mutation in a protein called fibrillin-1

Overview

- autosomal dominant connective tissue disorder.
- caused by a defect in the fibrillin-1 gene on chromosome 15
 - ⇒ Mutation of FBN1 that encodes Fibrillin-1.

- affects around 1 in 3,000 people.
- may occur as a spontaneous mutation, (1/3rd of cases), and this occurs more commonly to offspring of older males.

Features

- Skeletal
 - ⇒ tall stature with arm span to height ratio > 1.05
 - ⇒ high-arched palate
 - ⇒ arachnodactyly
 - ⇒ pectus excavatum
 - ⇒ pes planus
 - ⇒ scoliosis of > 20 degrees
 - ⇒ crowded teeth.
 - ⇒ Dural ectasia:
 - ballooning of the dural sac at the lumbosacral level
 - Dural ectasia affects around 60% of patients with Marfan's syndrome.
 - It may cause lower back pain associated with neurological problems such as bladder and bowel dysfunction.
 - ligamentous/joint laxity resulting in multiple joint dislocations, hypermobile joints
- Heart:
 - Dilation of the aortic sinuses (seen in 90%) which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%).
- Lungs: repeated pneumothoraxes
- Eyes:
 - ⇒ **Upwards** lens dislocation (superotemporal ectopia lentis) seen in 50% of patients
 - ⇒ Retinal detachment
 - ⇒ Blue sclera, myopia, early glaucoma, and early cataracts.

Diagnosis

- Unfortunately, DNA testing for fibrillin gene mutations, whilst helpful, cannot exclude a diagnosis of Marfan because a number of mutations exist (at least 130).
- Hence diagnosis is made on the major and minor features associated with the syndrome.

Prognosis & treatment:

- The life expectancy of patients used to be around 40-50 years.
- With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years.
 - ⇒ Treatment with β-blockers reduces the rate of aortic dilatation and the risk of rupture
- Aortic dissection and other cardiovascular problems remain the leading cause of death however.
- Pregnancy is associated with increased risk of aortic rupture.

A mutation of which gene is most closely associated with Marfan's syndrome?

- → FBN-1 mutation
 - FBN-1 gene mutation → Defect in fibrillin → Marfan's

Homocystinuria

Marfanoid skeletal abnormalities (tall and thin, elongated limbs, arachnodactyly) + mental retardation → Homocystinuria

Overview

- Autosomal recessive disease
- Caused by deficiency of cystathionine beta synthase results in an accumulation of homocysteine
 - cystathionine beta synthase is responsible for converting homocysteine to cystathionine. Cystathionine is later converted to cysteine,
 - so, patients who have this enzyme deficiency need to supplement their diets with exogenous cysteine.
 - Levels of homocysteine and methionine accumulate

Types

- Homocystinuria type 1 → a defect in cystathionine synthetase is responsible.
- Homocystinuria type 2 → defects in methylene tetrahydrofolate reductase
 - ⇒ However, individuals with this condition rarely survive the neonatal period or, if they survive longer than this, they often have more severe mental retardation.

Features

- · fine, fair hair
- · musculoskeletal: may be similar to Marfan's arachnodactyly etc
- · neurological: learning difficulties, mild to moderate mental handicap ,seizures
- · ocular: downwards (inferonasal) dislocation of lens
 - ⇒ The sudden visual deterioration could either be due to a thrombotic episode or to the lens dislocation associated with this condition.
- increased risk of arterial and venous thromboembolism (atherosclerosis, thrombosis, MI)
 - ⇒ the most common cause of death.
- · malar flush,
- livedo reticularis

Diagnosis

- made by the cyanide-nitroprusside test, which is also positive in cystinuria
 - ⇒ addition of sodium nitroprusside to urine → urine changes color to an intense red
- Guthrie test is used for screening the neonates for the presence of homocystinuria.

Treatment

- Dietary modification aim to: reduce intake of methionine and increase intake of cysteine.
- vitamin B6 (pyridoxine) supplements
 - ⇒ 50% of patients respond to large doses of pyridoxine (vitamin B₆)
- Folate and vitamin B12 supplements
 - ⇒ facilitate the conversion of homocysteine to methionine.
 - ⇒ homocysteine levels (homocysteinemia) are more commonly tested in diagnosis of Vitamin B12 Deficiency.

Homocystinuria VS Marfan's

	homocystinuria	Marfan's syndrome
inheritance	autosomal recessive autosomal dominan	
lens	downward lens dislocation	upward lens dislocation
dislocation		
aortic	heart rarely affected	aortic incompetence may
incompetence		occur
intellectual	mental retardation (nearly 50%)	normal
development		
livedo	seen due to the venous thrombosis in the small	NO
reticularis	vessels of the skin	
other	osteoporosis, recurrent thromboembolism;	flat feet, herniae, scoliosis;
principle	characteristic laboratory features:	there is a 50% reduction in
features	plasma methionine and homocystine levels are	life expectancy
	elevated, homocystine is excreted in the urine,	
	plasma cystine levels are reduced, positive urine	
	cyanide-nitroprusside test; response to treatment	
	with pyridoxine	

Fragile X syndrome

Overview

- Fragile X syndrome is a disorder affecting the <u>methylation</u> and expression of the fragile X mental retardation 1 gene.
- genetic inheritance → X-linked dominant with variable penetration
- Patients affected by fragile X syndrome usually have over 200 CGG trinucleotide repeats.

Features

- · moderate to severe mental retardation
- prognathism
- face: (long face, prominent forehead, large jaw (prognathism) and large ears
- macro-orchidism
 - ⇒ In post pubertal males, abnormally large testes are a distinctive feature.
- speech delays
- double-jointedness
- autistic symptoms,
- · occasional self-mutilation.
- · Otitis media, strabismus, and dental problems may be present
- hyperextensible joints
- · hypotonia,
- heart problems, including mitral valve prolapse.

Management

- Treatment focused on preventing common medical problems such as gastroesophageal reflux, sinusitis, and otitis media,+
- · speech, occupational, and physical therapy.

Trinucleotide repeat disorders

Anticipation in trinucleotide repeat disorders = <u>earlier onset</u> in successive generations

Definition

- Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides.
- These expansions are unstable and may enlarge which may lead to an earlier age of onset in successive generations - a phenomenon known as anticipation. In most cases, an increase in the severity of symptoms is also noted
- Friedreich's ataxia is unusual in not demonstrating anticipation

Examples (note dominance of neurological disorders):

- Fragile X (CGG)
- Huntington's (CAG)
- myotonic dystrophy (CTG)
 - ⇒ CTG repeats in the DMPK gene
- Friedreich's ataxia* (GAA)
 - ⇒ (*Friedreich's ataxia is unusual in not demonstrating anticipation)
- · spinocerebellar ataxia
- spinobulbar muscular atrophy
- Kennedy disease, also known as 'X-linked bulbospinal neuronopathy'
- dentatorubral pallidoluysian atrophy

Trinucleotide repeat disorders mnemonic:

Try (trinucleotide) hunting for my fried eggs (X).

Genetic anticipation

Anticipation: successive generations present with symptoms at an earlier age

- Definition: The 'classic' definition of anticipation is <u>earlier onset</u> in successive generations.
 However, in most cases, an increase in the severity of symptoms is also noted. If both options (earlier onset and sever symptoms) are presented, then the earlier onset should be chosen
- Example: A man aged 33 presents with features of Huntington's disease (depression, weight loss and choreiform movements). He informs you that his father had similar symptoms aged 50, his grandfather aged 75 and both deteriorated in terms of mobility and mental state, and eventually died.
- Occur in:
 - ⇒ Huntington's disease
 - ⇒ Mvotonic dvstrophv
 - ⇒ Fragile X syndrome

Polygenic diseases

- Definition:
 - ⇒ genetic disorder that is caused by the combined action of more than one gene.
 - ⇒ Because such disorders depend on the presence of several genes, they are not inherited as simply as are single-gene diseases.
- Examples:
 - ⇒ hypertension,
 - ⇒ coronary heart disease,

 - ⇒ Amyotrophic lateral sclerosis (ALS)

Lysosomal storage diseases

Definition

Lysosomal storage diseases are a group of inherited metabolic disorders caused by a
deficiency of specific enzymes. This causes an accumulation of abnormal substances that
are usually degraded within lysosomes, resulting in cell damage and death.

Risk factors

- · Ashkenazi ethnicity
- Male sex
 - ⇒ Fabry's disease is X-linked, but heterozygous females typically (>75%) do have symptoms, although less severe, more variable in expression, and at a later age of onset.

Key features

- Hyperacusis → Characteristic of Tay-Sachs disease.
- Optic atrophy or retinitis pigmentosa are seen in juvenile form of Tay-Sachs disease.
- hx of renal failure → Found in adult Fabry's disease.
- Hepatosplenomegaly → common in Gaucher's disease
- onset in adulthood (Fabry's, Gaucher's type 1, Pompe's)

Diagnosis

Enzyme assay (1st investigations to order)

Gaucher's disease

Gaucher

- Glucocerebrosidase deficiency
- Glucocerebroside accumulation

Features involve multiple systems: Blood (pancytopaenia , anaemia, recurrent infections,) bones, hepatosplenomegaly, lung (cough) → think of Gaucher's disease

Pathophysiology

Autosomal recessive mutation in the glucocerebrosidase (GBA) gene located
on chromosome 1 → Deficiency of β-glucocerebrosidase → accumulation of
glucocerebroside (sphingolipid found in cell membranes that can accumulate in the
lysosome of macrophages) in the brain, liver, spleen, and bone marrow (i.e., Gaucher
cells).

Epidemiology

- Gaucher's disease is the most common lysosomal storage diseases.
- About one in 100 people in the United States are carriers of the most common type of Gaucher disease (**type I**).
- The carrier rate among Ashkenazi Jews is 8.9% while the birth incidence is one in 450.

Consequences

- Parkinson's disease is more common in Gaucher's disease patients (the most commonly known genetic risk factor for Parkinson's)
- Cancer risk may be increased, particularly myeloma.

Types

- GD type I (Chronic non-neuropathic; adult Gaucher disease)
 - **⇒** Most common form
 - ⇒ Associated with a normal lifespan
- GD type II (Acute neuropathic; infantile Gaucher disease)
 - ⇒ typically begins within 6 months of birth
 - ⇒ Symptoms include progressive brain damage, spasticity and seizures.
 - ⇒ carries the worst prognosis, affected children **usually die by age two**.
- GD type III (Subacute neuropathic; juvenile Gaucher disease)
 - ⇒ can begin at any time in childhood or even in adulthood
 - ⇒ characterized by slowly progressive, but milder neurologic symptoms compared to type II.
 - ⇒ Patients often live into their early teen years and adulthood

Features

- Hepatosplenomegaly (massive splenomegaly)
- Bone pathology (bone crises, osteoporosis, aseptic necrosis) the chief complaint is
 of bone pain in an adult.
- Blood abnormalities: anemia, thrombocytopenia
- diffuse infiltrative pulmonary disease
- Growth delays
- Yellowish-brown skin and scleral pigmentation (Characteristic yellow or yellow-brown papules (pingueculae) develop at the sclerocorneal junctions).

Diagnosis

- Enzyme analysis (Enzyme studies of blood leucocytes) → Reduced qlucocerebrosidase activity in leukocytes or fibroblasts
- Accumulation of glucocerebroside in leukocytes or fibroblasts
- Gaucher cell: lipid-rich macrophages with an enlarged cytoplasm with inclusions that resemble crumpled tissue paper on microscopy

Treatment

· Recombinant glucocerebrosidase.



The slide shows yellow papules (pingueculae) in the cornea; these are characteristic of Gaucher disease.

Common exam questions

- Features of anaemia, recurrent pneumonia, bone pain and hepatosplenomegaly.
 Which of the following is the most likely diagnosis?
 - ⇒ Gaucher's disease
- Features of anaemia, recurrent pneumonia, bone pain and hepatosplenomegaly
 .Which of the following is the most likely enzyme deficiency found in this patient?
 - ⇒ Glucocerebrosidase

Gaucher disease causes massive splenomegaly

Fabry's disease

Pathophysiology (a lysosomal storage disorder)

 X-linked recessive mutation → α-Galactosidase A deficiency → accumulation of trihexoside ceramide (a glycolipid found in multiple body tissues) in the endothelium of vessels, in the epithelium of many organs, and in smooth muscle cells → disorder affecting many organ systems.

Epidemiology

- Typical onset is during childhood but may also appear in 60–80-year-old adults
- · Mainly affects boys

- Early features
 - Peripheral neuropathy: Periodically occurring dysesthesia in the hands and feet caused by small fiber neuropathy, which manifests as burning pain (Fabry crises)
 - ⇒ Anhidrosis or hypohidrosis (decreased sweating)
 - Angiokeratomas (warty skin lesions with telangiectasia and hyperkeratinized covering)
 - □ Corneal clouding
 - ⇒ Cataract

Late features

- ⇒ Restrictive cardiomyopathy
- ⇒ Cerebrovascular lesions (TIA and stroke)
- ⇒ Fabry nephropathy, causing progressive renal failure (the first manifestation of renal insufficiency in Fabry disease is <u>proteinuria</u>.)

The disorder has three distinct clinical entities:

- Classical presentation in the male homozygote with early presentation in childhood angiokeratomas, heart failure, cataracts and renal disease
- 2. Male homozygotes with atypical presentation in adulthood with proteinuria, acroparaesthesia, angiokeratomas and cardiomegaly
- 3. Female heterozygotes can present again in adulthood with similar mild symptoms.
 - An X linked recessively inherited condition can exist in female carriers who may exhibit mild to moderate symptoms. This is due to variable expression according to random X inactivation of the affected gene in embryogenesis

most common symptoms → peripheral neuropathy, angiokeratomas, and hypohidrosis.

Diagnosis

- Absent or deficient levels of alpha-galactosidase A in leucocytes, plasma or cultured fibroblasts.
- Gene analysis of alpha-galactosidase A (GLA) gene (the gold standard for the diagnosis)
- Slit-lamp examination of the cornea → microscopic lipid deposits
- Microscopy of the spun urine sediment may demonstrate 'Maltese cross' lipid globules

In Fabry disease, tissue accumulation of which is most likely to occur?

Trihexosyl ceramide

Treatment

• Enzyme replacement therapy with α -galactosidase A

Mucopolysaccharidoses (MPS) (Hurler's & Hunter's syndromes)

Pathophysiology

Mutations in lysosomal enzymes → impaired breakdown of glycosaminoglycans →
 Accumulation of glycosaminoglycans, i.e., heparan sulfate (HS) and dermatan sulfate (DS)

Features

- Occur in both conditions (typically milder in Hunter syndrome):
 - ⇒ Developmental delay
 - ⇒ Facial dysmorphism: frontal bossing, elongated skull, flattened nasal bridge, broad nasal tip, thickened gingiva, anteverted nostrils, constant nasal discharge, spaced and protruded eyes.
 - ⇒ Airway obstruction
 - ⇒ Hepatosplenomegaly

Diagnosis

- Increased urinary levels of dermatan sulfate (DS) and heparan sulfate (HS)
- Enzyme assay to confirm specific enzyme deficiency (definitive test)

Treatment

- Enzyme replacement therapy
- Bone marrow transplantation

	Hurler syndrome (mucopolysaccharidosis type I)	Hunter syndrome (mucopolysaccharidosis type II)
Inheritance	Autosomal recessive	X-linked recessive
Pathophysiology	Deficiency of α-L-iduronidase (enzyme responsible for the hydrolysis of glycosaminoglycans)	Deficiency of iduronate-2-sulfatase
Features	Corneal cloudingInguinal hernia	 Aggressive behavior, Hyperactivity No corneal clouding Carpal tunnel syndrome

Which feature suggests a diagnosis of Hurler's syndrome rather than Hunter's syndrome?

→ Cloudy cornea.

Hunter syndrome presents as Hurler syndrome, but patients with Hunter syndrome have normal vision and aggressive behavior.

Glycogen storage disorders (GSD)

Key feature of glycogen storage disorders:

- Tay-Sachs commonly has a 'cherry red spot' macula
- Pompe disease leads to cardiomyopathies
- McArdle's disease leads to rhabdomyolysis after exercise and lactic acidaemia
- Von Gierke disease leads to hypoglycaemia and hepatomegaly

Pompe trashes the Pump (heart)

Glycogen

- Glycogen is the storage form of carbohydrate, found predominantly in muscle and liver.
- Chains of glucose residues are linked by alpha-1,4 glycosidic bonds, i.e. between the
 first carbon of one glucose and the fourth carbon of the next. Branches occur about
 every ten residues, and are formed by alpha-1,6 glycosidic linkages.
- Glycogen synthesis and degradation occur at the tips of branches, with the branching structure increasing the number of sites at which glucose residues can be added or removed.

Pompe's disease or acid maltase deficiency (glycogen storage disorder type 2): is a deficiency in alpha-glucosidase. It produces a myopathy, restrictive cardiomyopathy and hepatomegaly.

Glycogen storage disorders:

- Muscle involvement (muscle glycogenoses): Types II, III, IV, V
- Liver involvement (liver glycogenoses): Types I, III, IV
- Types III and IV (late-onset type) may present with both muscle and liver involvement
- NO liver involvement → V

Autosomal recessive

- All types of glycogen storage diseases result in abnormal metabolism and product accumulation within cells.
- Type IV (Andersen's disease) is the only one GSD involved in Glycogen Synthesis. The rest
 are involved in Glycogen degradation.

Diagnosis

• Periodic acid-Schiff stain is helpful in diagnosing glycogen storage disorders.

Type I (Von Gierke's disease)

- Relative frequency: ~25%
- Deficient enzyme
 - ⇒ Type 1a → Glucose-6-phosphatase
 - Role of the enzyme → Hydrolysis of glucose-6-phosphate to glucose and inorganic phosphate
 - ⇒ **Type 1b** → Glucose-6-phosphate translocase
 - Role of the enzyme → Transport of glucose-6-phosphate into the endoplasmic reticulum where it is hydrolyzed by glucose-6-phosphatase
- Characteristic features
 - ⇒ Hepatomegaly
 - ⇒ Severe fasting hypoglycemia, mild ketosis
 - ⇒ Severe hyperlipidemia → doll-like facies
 - ⇒ Hyperuricemia
 - ⇒ Lactic acidosis
 - ⇒ Anemia
 - ⇒ Failure to thrive

Type II (Pompe's disease)

- Relative frequency: ~15%
- Deficient enzyme: Lysosomal acid maltase deficiency
- Role of the enzyme: Glycogenolysis within the lysosome
- · Characteristic features
 - ⇒ Hypertrophic cardiomyopathy and/or conduction blocks
 - ⇒ Proximal myopathy
 - ⇒ Macroglossia
 - ⇒ Failure to thrive

Type III (Cori's disease)

- Relative frequency: ~25%
- Deficient enzyme: debranching enzyme (alpha-1,6-glucosidase).
- Role of the enzyme: Glycogenolysis
- Characteristic features
 - ⇒ Generalized muscle weakness and/or cramps
 - ⇒ Hepatomegaly
 - ⇒ Possibly cirrhosis (ascitis, splenomegaly)
 - ⇒ Mild, fasting hypoglycemia and ketosis
 - ⇒ Hyperlipidemia

Type IV (Andersen's disease)

- Relative frequency: ~3%
- Deficient enzyme: Glycogen branching enzyme
- Role of the enzyme: Glycogenesis
- · Characteristic features
 - ⇒ Proximal myopathy
 - ⇒ Hepatomegaly
 - ⇒ Possibly cirrhosis (ascites, splenomegaly)

Type V (McArdle's disease)

- Relative frequency: ~2%
- Deficient enzyme: Muscle phosphorylase (myophosphorylase)
- · Role of the enzyme: Glycogenolysis
- Characteristic features
 - ⇒ Generalized muscle weakness, exercise intolerance (with a second wind phenomenon),
 - ⇒ Rhabdomyolysis and myoglobinuria

McArdle's disease (Type V glycogen storage disease)

Often presents in adolescence with exercise intolerance, cramps and weakness

A history of painful muscle cramps that occur within a few minutes of initiating activity and which subside rapidly with rest, in conjunction with a raised serum CK, is highly suggestive of McArdle's disease

Pathophysiology

Autosomal recessive mutation in myophosphorylase (PYGM) gene on chromosome 11 →
myophosphorylase deficiency (myophosphorylase is involved in the breakdown of
glycogen to glucose) → unable to release glucose from glycogen in muscle (decreased
muscle glycogenolysis).

Features

- Muscle pain and stiffness following exercise (reversible)
 - ⇒ in the first few minutes of activity.
 - ⇒ Characterised by 'second wind' phenomenon
 - after about 8 minutes most patients achieve a 'second wind' and can then continue exercise with less difficulty.
 - Second wind is a phenomenon in distance running, such as marathons (an athlete who is too tired to continue suddenly finds the strength to press on at top performance with less exertion).
 - Mechanism → metabolic switch
 - When non-aerobic glycogen metabolism is insufficient to meet energy demands, physiologic mechanisms utilize alternative sources of energy such as fatty acids and proteins via aerobic respiration.
 - muscle fibers use fat as a source of energy.

Investigations

- Creatine kinase levels are elevated in more than 90%
- NO increase in venous lactic acid levels following exercise testing.
- Urine study → Myoglobinuria following exercise
- Muscle and/or liver biopsy →↑glycogen→ PAS-positive granules (initial tests)
- DNA testing for the gene defects (Gene sequencing): the gold standard for the diagnosis

Management

- No specific treatment
- Dietary therapy (e.g., uncooked corn starch, glucose preparations) with the aim of preventing hypoglycemia and/or muscle symptoms
- Foods rich in fructose and galactose should be avoided in patients with GSD type I
- Advised to ingest snacks containing sucrose before exercise.
- Tourniquets should not be used during operative procedures

The exertional thigh cramps, the presence of myoglobin and change in colour of urine after exercise suggests glycogen storage disease type V - McArdle's syndrome. the next most appropriate investigation → Muscle biopsy which reveals subsarcolemmal deposits of glycogen appearing at the periphery of fibres.

Linkage disequilibrium

- Linkage disequilibrium is the non-random association of alleles at different loci in a given population.
- Loci are said to be in linkage disequilibrium when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly.
- Consider the scenario of two separate genetic loci A and B, where each locus carries two
 possible alleles. If these two loci A and B are in linkage disequilibrium → An individual
 with locus A is likely to have locus B
- Linkage disequilibrium almost always, occurs between alleles at genetic loci that are closely linked in the genome.

Imprinting

Definition

- imprinting is a phenomenon by which certain genes are expressed in a parent-of-originspecific manner.
 - ⇒ the term 'imprinting' refers to → Differential expression of alleles contingent on their parental origin
 - If the allele inherited from the father is imprinted, it is thereby silenced, and only the allele from the mother is expressed.
 - If the allele from the mother is imprinted, then only the allele from the father is expressed.

Mechanism

- poorly understood but does involve DNA methylation.
- Disease may occur as a result of a defect in one allele if the other allele is imprinted and hence not expressed.

Examples

- diseases involving genomic imprinting include:
 - ⇒ Prader–Willi syndrome (paternally imprinted)
 - ⇒ Angelman syndrome (maternally imprinted)

Prader-Willi syndrome

Deletion of chromosome 15

- Prader-Willi paternal
- · Angelman syndrome maternal

Overview

- Prader-Willi syndrome is an example of **genetic imprinting** where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:
 - ⇒ Prader-Willi syndrome if gene deleted from father
 - ⇒ Angelman syndrome if gene deleted from mother
- Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome 15. this may be due to:
 - ⇒ Microdeletion of paternal 15q11-13 (70% of cases)
 - ⇒ Maternal uniparental disomy of chromosome 15
- The mode of inheritance is → Non-Mendelian

Features

- Hypotonia during infancy
- Dysmorphic features
- Short stature (Growth hormone deficiency)
- · Hypogonadism and infertility
 - ⇒ (risk factor for osteoporosis)
- Cryptorchidism (undescended testis)
- Learning difficulties
- Childhood obesity due to Hyperphagia (abnormally desire for food → overeating → obesity)
- · Behavioural problems in adolescence
- · Associated with elevated ghrelin
 - ⇒ Ghrelin is a hormone produced in the fundus of the stomach and in the pancreas
 - ⇒ Ghrelin levels increase before meals and decrease afterwards
 - Receptors for ghrelin are found in the arcuate nucleus and the hypothalamus

Treatment

- Administration of growth hormone and sex hormones (testosterone) is the treatment of choice
- Calorie restriction

MRCPUK-part-1-September 2017 exam: Which one of the following is the most common genetic cause of Prader-Willi syndrome?

→ Microdeletion of the paternal 15q11-13

Chromosome 15 is implicated in Prader-Willi, Angelman, and Marfan syndromes.

Angelman syndrome

Overview

- Angelman syndrome is a genetic condition characterized by a mutation on the maternal copy of chromosome 15.
- occurs as a result of a phenomena known as genomic imprinting.
- The imprinted copy of the gene is silenced through methylation or histone modification.
- Normally, certain paternal alleles on chromosome 15 are silenced and only the
 maternal alleles are expressed. However, in Angelman syndrome, the maternal alleles are
 mutated. Hence, the patient will have disease since only the mutated maternal alleles are
 active.

Features

- Developmental delay
- Intellectual disability
- Seizures, Ataxia
- Unprovoked laughter
- Large mouth with tongue protrusion.
- · Hypo-pigmentation with blond hair

Diagnosis

genetic studies showing loss of function of the <u>UBE3A</u> gene.

Mutations

Missense mutation

- ⇒ substitution in one amino acid in a protein
- ⇒ e.g. glutamic acid is substituted by valine in sickle-cell disease

Nonsense mutation

the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.

Insertion mutation

⇒ changes the number of DNA bases in a gene by **adding a piece of DNA**. As a result, the protein made by the gene may not function properly.

Frameshift mutation

- ⇒ insertions or deletions of nucleotides
- ⇒ e.g: cystic fibrosis

Point mutation

- ⇒ a change in a single nucleotide
- ⇒ e.g: C282Y mutation responsible for haemochromatosis

Splicing mutation

- ⇒ results in larger nonfunctional protein
- ⇒ e.g: β-thalassemia

Large Segment Deletion

- ⇒ Unequal crossover at meiosis results in loss of large segment of DNA
- ⇒ Loss of function mutation
- ⇒ e.g., α-thalassemia (deletion of α-globin gene)

Termination mutation

- ⇒ generation of a premature stop codon
- ⇒ e.g: Hurler syndrome

Chromosome abnormality

 Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis.

Types

- Numerical disorders
 - ⇒ called **aneuploidy** (an abnormal number of chromosomes), occurs when an individual either is:
 - missing a chromosome from a pair (monosomy)
 - e.g: Turner syndrome, (born with only one sex chromosome, an X).
 - has more than two chromosomes of a pair (trisomy, tetrasomy, etc.).
 - e.g: Down syndrome (trisomy 21)
 - ⇒ Unbalanced autosomal translocation
 - most likely to cause a severe phenotype
 - As a rule, the clinical effects of a chromosome abnormality reflect the amount of imbalance of genetic material. For example: all autosomal monosomies and most autosomal trisomies are incompatible with life, the exceptions being trisomy 13 (Patau syndrome), trisomy 18 (Edward syndrome) and trisomy 21 (Down syndrome); only the last of these carries a reasonable life expectancy.
 - **⇒** Sex chromosome aneuploidy:
 - This is associated with comparatively <u>less severe phenotypes</u>, e.g. Klinefelter syndrome (XXY) and Turner syndrome (XO).
- Structural abnormalities: e.g.
 - ⇒ Duplications:
 - A portion of the chromosome is duplicated, resulting in extra genetic material.
 - e.g: Charcot-Marie-Tooth disease type 1A, caused by duplication of the gene encoding peripheral myelin protein 22 (PMP22) on chromosome 17.

List of common Chromosomal disorders:

Chromosome	disorders
Chromosome 1	variegate porphyria
chromosome 3	von Hippel Lindau (VHL)
Chromosome 4	Polycystic Kidney Disease (PKD2) Huntington's disease Achondroplasia
Chromosome 6	hereditary haemochromatosis
Chromosome 7	Cystic Fibrosis
Chromosome 9	Fredrich's ataxia
Chromosome 11	Sickle Cell Disease Beta-Thalassemia
Chromosome 12	Phenylketonuria von Willebrand's disease
Chromosome 13	Patau Syndrome. Wilson Disease. retinoblastoma
Chromosome 15	Marfan's Syndrome Angelman Syndrome Prader-Willi Syndrome Tay-Sachs Disease.
Chromosome 16	Polycystic Kidney Disease (PKD1) alpha- Thalassemia
Chromosome 17	Celiac Disease. Charcot-Marie-Tooth Disease. Neurofibromatosis (NF1)
Chromosome 18	Edward Syndrome
Chromosome 19	Myotonic Dystrophy
Chromosome 21	Down Syndrome
Chromosome 22	DiGeorge Syndrome. Neurofibromatosis (NF2)

McCune-Albright syndrome (MAS)

McCune-Albright syndrome:

- Triad of patchy skin pigmentation, bone abnormalities, and endocrine abnormalities.
- McCune-Albright syndrome is a form of mosaicism
- Due to a mutation in the GNAS1 gene

Notes & Notes

For MRCP part 1 & 11

By

Dr. Yousif Abdallah Hamad

Basic science Biostatistics & EBM

Updated

Significance tests

Null hypothesis (H₀)

- A null hypothesis (H₀) states that two treatments are equally effective (and is hence negatively phrased).
- A significance test uses the sample data to assess how likely the null hypothesis is to be correct.
- The null hypothesis is always that there is no difference between the variables we would like to test for a difference.
- For example: 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis (H₁)

• is the opposite of the null hypothesis, i.e. There is a difference between the two treatments **P value**

- The **p value** is the probability of obtaining a result by chance at least as extreme as the one that was actually observed, assuming that the null hypothesis is true.
- It is therefore equal to the chance of making a type I error (see below).
- the p-value is the probability of obtaining the observed results or results which are more extreme if the null hypothesis is true
- Example: if p=0.03. What does 'p=0.03' mean?
- It means →the probability that a difference between the two sample groups occurred by chance is 3%

Statistical errors

- Two types of errors may occur when testing the null hypothesis
 - **1.** type I:
 - the null hypothesis is rejected when it is true,
 - " 'the null hypothesis is falsely rejected'.
 - i.e. Showing a difference between two groups when it doesn't exist,
 - a false positive.
 - This is determined against a preset significance level (termed alpha).
 - As the significance level is determined in advance the chance of making a type I error is not affected by sample size.
 - It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance. i.e. the result is just a statistical fluke.
 - 2. type II:
 - the null hypothesis is accepted when it is false,
 - " 'the null hypothesis is falsely accepted'.-
 - i.e. Failing to spot a difference when one really exists,
 - a false negative.
 - The probability of making a type II error is termed beta.
 - It is <u>determined by both sample size</u> and alpha. This can happen if the sample size is too small.
 - Increasing the sample size reduces the standard error, meaning the estimate is more precise and the probability of a type-2 error is reduced.
 - This type of error <u>can be avoided by making explicit power calculations before</u> embarking on any study. This will answer the question 'if I am studying an

outcome that occurs in (say) 20% of a conventionally treated group and want to show a (say) halving in the rate of this outcome, then how many patients do I need to study?'

	Study accepts H ₀	Study rejects H ₀
Reality H ₀		Type 1 error (alpha)
Reality H ₁	Type 2 error (beta)	Power (1 - beta)

HYPOTHESIS TESTING OUTCOMES		Reality		
		The Null Hypothesis Is True	The Alternative Hypothesis is True	
R e s e	The Null Hypothesis Is True	Accurate 1 - α	Type II Error β	
a r c h	The Alternative Hypothesis is True	Type I Error	Accurate 1 - β	

Error: type I (alpha) vs. type II (beta)

Type I (Alpha) Error: "There Is An Effect" where in reality there is none.

The power

- The power of a study is the probability of (correctly) rejecting the null hypothesis when it is false, i.e. the probability of detecting a statistically significant difference
 - ⇒ power = 1 the probability of a type II error
 - ⇒ power can be increased by increasing the sample size
- As the power decreases, type II error (= 1-power) will increase. Therefore, the chance
 of type II error will increase if the same sample size is used.
- The statistical power will decrease if the standard deviation increases.
- Power of the study' refer → The probability of a statistically significant treatment effect if the true treatment difference is at a prespecified level
- Power is determined by sample size, effect size, and its standard error.
- The statistical significance of a result is the probability ('p value') that the observed relationship (eg between variables) or a difference (eg between means) in a sample occurred by pure chance and that in the population from which the sample was drawn, no such relationship or differences exist
- The sample size can be reduced if the level of significance is increased.
- The power increases with the set level of significance, if other variables remain the same.

Significance tests: types

Correlation

- · parametric (normally distributed): Pearson's coefficient
- non-parametric: Spearman's coefficient
- The type of significance test used depends on whether the data is <u>parametric</u> (something which can be measured, usually normally distributed) or non-parametric
 - ⇒ Parametric tests (the data follow normal distribution) (quantitative variables)
 - Student's t-test paired or unpaired*
 - Pearson's product-moment coefficient (Pearson correlation coefficient)
 - used to assess <u>correlation</u> (strength of association) between two variables
 - ⇒ Non-parametric tests
 - Mann-Whitney U test unpaired data
 - used to compare <u>medians or rank</u> orders of <u>two groups</u> with nonnormal distribution.
 - Wilcoxon signed-rank test:
 - compares two sets of observations on a single sample
 - The data in the study is <u>non-parametric</u>, <u>paired</u> and comes from the same population.
 - chi-squared test:
 - used to compare <u>proportions</u> or <u>percentages</u> (eg: prevalence)
 between two categorical variables
 - for example, comparing the proportion of children developing measles between a group receiving a new measles vaccine and a group not given the vaccine
 - Should be used for 2 independent samples.
 - Spearman, Kendall rank:
 - measures the <u>correlation</u> between the ranks of <u>two</u> variables which do not follow a normal distribution.
 - compares <u>ranks</u> and not values, such as the perception of pain (<u>ranked</u> on a scale of 1-10)

In a scenario looks at whether the values are correlated, and the data is non-parametric, (e.g. pain scale), Spearman's rank correlation coefficient should be used.

 Paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

Choosing the appropriate test

- Choosing of a test to examine a statistical problem depends upon the scale of measurement (nominal, ordinal, interval, ratio) and the type of question being asked
- a non-parametric test would give less power

Student's t-test

- Paired t test
 - ⇒ Compares a <u>single measure</u> (variable) recorded <u>on a single group</u> of individuals on two different occasions.
 - ⇒ Is used to compare **means in a single sample**, <u>for example, before and after</u> treatment.
 - ⇒ comparing means (not proportions) in the same subjects
 - paired t-test is used to compare <u>post</u>-treatment <u>and pre</u>-treatment result of a <u>single group</u>.
 - ⇒ eg: the same subject measured before and after a process change, or the same subject measured at different times.
 - ⇒ As both sets of measurements were made on the same patients, the measurements are not independent
- Unpaired t-test (independent sample t-test)
 - ⇒ is the most appropriate statistical test to compare means of two independent samples.
 - compare the means of two different populations
 - ⇒ An independent sample *t*-test may be used in a study of two independent treatment groups, and the sample sizes are relatively large (>30 in each group) and the variable is **Normally distributed**.
 - ⇒ eg: Blood pressure is a continuous variable which is normally distributed; as such Student's *t* test is the most appropriate way to test for <u>differences in the mean BPs</u> <u>between the two groups</u>.
 - ⇒ For example, suppose we are evaluating the effect of a medical treatment, and we enroll 100 subjects into our study, then randomly assign 50 subjects to the treatment group and 50 subjects to the control group. In this case, we have two independent samples and would use the unpaired form of the *t*-test.
 - ⇒ eg: 2 groups (treatment group & placebo group) In a randomised controlled trial of drug A for treatment of hypercholesterolemia

Log-rank test

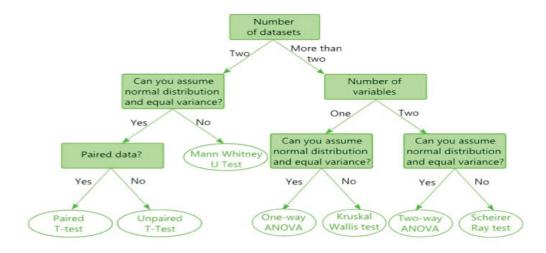
- Is the most appropriate test to compare two survival curves with censored data.
- Log-rank test should be used to compare survival data between two groups, but not compare median survival. Mean survival is not known unless all patients have died.
- If a question presented survival data and some observations are censored(ex: not came for follow up) and the outcomes are not known. We need to use survival analysis for such data and the log-rank test is the appropriate test to use to compare survivals in two independent groups.
- can be used to test the difference in relapse rate between the two groups

McNemar's test

- is applied to binary data, but is only applicable to paired data, used to compare proportions
- McNemar's test is used to compare paired samples either case control studies where each case is matched to a control, or to studies where two treatments are given to matched subjects.
- It cannot be used where the sample size differs.
- is used to test for agreement of repeated observations.

Regression techniques

- · are used to predict the value of one variable based on the other
- Multiple regression
 - ⇒ is used to analyse the relationship between one dependent variable and one or more independent variables
- Logistic regression (Log regression analysis)
 - ⇒ It is used to describe the relationship between one dependent binary variable and one or more metric independent variables.
 - ⇒ It is commonly used to assess plasma concentrations of a drug as it allows examination of the relationship between possible confounding factors such as renal function or age.
 - ⇒ This would allow us to determine whether one variable is dependent on another, ex: in case whether drug concentration was dependent on body surface area.
 - ANOVA (analysis of variance) is an example of logistic regression analysis.
 - is a statistical test which tests for co-variance between populations and is useful when variables such as age, sex or race may be expected to affect the treatment's effectiveness.
 - tests for a difference in mean values between a number of groups
 - Is the most appropriate to compare the means of more than two groups. (used for more than two means)
 - One-way analysis of variance is identical mathematically to the unpaired Student t-test when just two groups are being compared.
 - The one-way (analysis of variance) (ANOVA) compares the means of the groups
 - The means should be presented with confidence intervals to give the reader an idea of whether the differences between the groups were significant
- The Cox (proportional odds) regression (Cox proportional hazards regression):
 - this method was devised specifically for the type of study in which many patients fail to reach the end-point (ie in statistical terms, are 'censored') and in which follow-up time varies.
 - ⇒ Cox regression is designed specifically for the analysis of time to an event occurring.



Parametric tests and analogous nonparametric procedures

Analysis Type	Example	Parametric Procedure	Nonparametric Procedure
Compare means between two distinct/independent groups	Is the mean systolic blood pressure (at baseline) for patients assigned to placebo different from the mean for patients assigned to the treatment group?	Two-sample t-test	Wilcoxon ranksum test
Compare two quantitative measurements taken from the same individual	Was there a significant change in systolic blood pressure between baseline and the six-month followup measurement in the treatment group?	Paired t-test	Wilcoxon signedrank test
Compare means between three or more distinct/independent groups	If our experiment had three groups (e.g., placebo, new drug #1, new drug #2), we might want to know whether the mean systolic blood pressure at baseline differed among the three groups?.	Analysis of variance (ANOVA)	Kruskal-Wallis test
Estimate the degree of association between two quantitative variables	Is systolic blood pressure associated with the patient's age?	Pearson coefficient of correlation	Spearman's rank correlation

- Categorical variables are not continuous, e.g. drug / placebo, dead / alive. They should be
 described as percentages or proportions and compared with a Chi-squared test.
- Normally distributed continuous data should be described as mean and standard deviation and compared with a Student's t-test.
- Skewed continuous data should be described as median and range and compared using a test such as the Wilcoxon rank-sum test or the Mann-Whitney U-test.

MRCPUK-part-1-May-2017 exam: A study is designed to assess severity of snoring before and after using a new mandibular device. What is the most appropriate statistical test to apply to this data?

→ Wilcoxon signed-rank test

Normal distribution

- The normal distribution is also known as the Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements
- Properties of the Normal distribution
 - symmetrical i.e. Mean = mode = median
 - **♦** 68.3% of values lie within 1 SD of the mean
 - **▶** 95.4% of values lie within 2 SD of the mean
 - **▶** 99.7% of values lie within 3 SD of the mean
 - this is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
 - the range of the mean (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

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MRCPUK-part-1-January 2019 exam: A study is designed to assess the efficacy of a new antihypertensive drug. Two groups of patients are randomly assigned, one to take the established drug for 3 months whilst the other takes the new drug for 3 months. blood pressure is measured before and 3 months. After period off medication the drug swapped around and again, blood pressure is measured before and 3 months later. Which one of the following significance tests is it most appropriate to apply?

→ Student's paired t-test (comparing parametric data from the same patients (they swapped medication halfway through the study))

Standard deviation

SD = square root (variance)

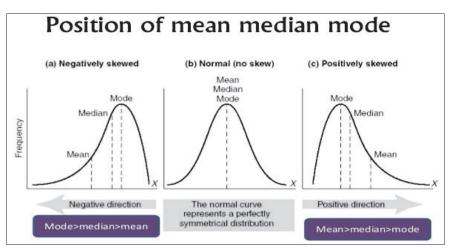
Remember that around two-thirds of values lie within 1 SD of the mean, one-third will therefore lie outside 1 SD, and half of these (one-sixth) will be less than 1 SD below the mean

- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- It is a measure of the spread of the sample distribution
- SD = square root (variance)
- The standard deviation is a sort of average of the deviations of each observation from the mean, whereas the range is simply the difference between the largest and smallest observations.
- The standard deviation is affected by outliers and would be larger than expected if outliers are present
- If the data are skewed, the standard deviation will tend to overestimate the spread in the data
- If the standard deviation is reduced, the sample size required is smaller.
- If SD increased the power of study is reduced.
- The standard deviation would give the best estimate of a spread of a measurement about the mean
- Variance is the square of standard deviation. Standard deviation is the square root of variance.

Skewed distributions

Skewed distributions

- alphabetical order: mean median mode
- '>' for positive, '<' for negative
- Normal (Gaussian) distributions: mean = median = mode (bell-shaped)
- Positively skewed distribution: mean > median > mode
- Negatively skewed distribution mean < median < mode
- To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'



- Mean, median and mode are measures of central tendency
- Descriptive statistics provide mean, median and mode values for a distribution

Example: The annual numbers of reported cases of leptospirosis in the USA over the 5-year period from 1985 to 1990 were: 2, 1, 3, 4, 1, . What was the mean, median and modal number of cases per year?

Answer:

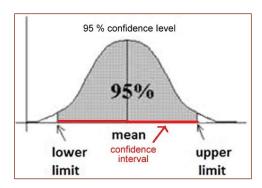
- The mean is found by summing all the values and dividing by 5; this gives a mean = 11/5=2.2
 - ⇒ The mean is the average value of observations, and therefore very sensitive to extreme values in a distribution
 - ⇒ If the mean is greater than the median, this indicates a positive skew.
- For the median and mode → rewrite the values in ascending order: ie 1.1.2.3.4.
- The median is the middle value when the values are placed in order = 2
 - ⇒ For an even number of values it is halfway between the two middle values,
 - ⇒ If you forgot to sort the values before looking for the middle value, you will have got the incorrect answer = 3
 - ⇒ The median is the observation that divides the frequency distribution by half and is equal to the 50th centile (lies exactly between each end of a range of values)
 - ⇒ It responds to the number of extreme observations but not their value, and therefore is useful as a measure of central tendency in extremely skewed distributions
 - ⇒ In a normal distribution the median equals the mean
- The mode is the most common value; this is → 1, which occurs twice, whereas all other values occur only once
 - ⇒ mode is the most commonly observed value

- The distribution sample means will be normally distributed even if the population values are not normally distributed.
- The random sampling distribution of means would always tend to be normal, irrespective of
 the population distribution for which the samples were drawn. Hence, even if the population
 distribution is skewed or in any non-normal distribution, the sample means would be
 normally distributed.'
- the mean of the random sampling distribution of means is equal to the mean of the original population.
- In a distribution skewed by the presence of a number of positive outliers
 → Mean increases, median may increase, mode remains the same

Confidence interval and standard error of the mean

Standard error of the mean = standard deviation / square root (number of patients)

- Definition of confidence interval
 - ⇒ a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable.
 - ⇒ The specified probability is called the <u>confidence level</u>, and the end points of the confidence interval are called the <u>confidence limits*</u>
 - ⇒ in simpler terms: a range of values within which the true effect of intervention is likely to lie
- A confidence interval is needed for almost all statistical estimates, including sensitivity or specificity of a diagnostic test.
- If the confidence interval includes the number 1,→ the trial did not find a statistically significant difference between the variables (this does not mean there was no difference)
 - ⇒ This means the association is not statistically significant and therefore the p value should be above 0.05.



Key point

- A 95% confidence interval:
 - ⇒ Most commonly, the 95% confidence level is used.
 - ⇒ What is the best interpretation of the 95% confidence interval?
 - We are 95% confident that the mean in the value is between confidence limits
 - ⇒ confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

- ⇒ A 95% confidence interval means that there is only a 5% chance that the true mean value for the variable lies outside the ranges quoted
- ⇒ The 95% confidence limits will be the mean plus or minus 1.96 standard errors
 - lower limit = mean (1.96 * SEM)
 - upper limit = mean + (1.96 * SEM)
- ⇒ For example, in a study the mean height in a sample taken from a population is 183cm. You know that the standard error (SE) (the standard deviation of the mean) is 2cm. This gives a 95% confidence interval of 179-187cm (+/- 2 SE).
- ⇒ meaning that there is a 5% chance that the true population mean is not included in this range, in other words a 95% chance that the true population mean is included within this range
- ⇒ If the 95% confidence interval does not include 0 (zero), the difference is statistically significant
- ⇒ If the p value is less than 0.05, → statistically significant → the 95% confidence interval should not include 0.
- Standard error of the mean (SEM)
 - ⇒ The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean
 - ⇒ SEM = SD / square root (n)
 - where SD = standard deviation and n = sample size
 - therefore, the SEM gets smaller as the sample size (n) increases
 - ⇒ standard error of the mean → Gets smaller as the sample size increases
 - Increasing the sample size will reduce the standard error of the mean and the width of the confidence interval.
 - ⇒ The standard error is → Smaller than the standard deviation

Assessment of significance (is the result statistically significant?)

- If confidence interval does not include 1, this means the association is statistically significant and therefore the p value should be below 0.05.
- A narrow confidence interval emphasises the significance of the result, but it is the p-value that describes significance, not the confidence interval around it.
- If there is no significant P-value given in the question, we can conclude that the
 association in the question is significant if the 95% confidence interval is very
 narrow (its range does not include the value 0). (e.g: 95% confidence interval 2 to 8)

Confounding variable

- Is an extraneous **variable** in a statistical model that correlates (directly or inversely) with both the dependent **variable** and the independent **variable**.
- To give a hypothetical **example** of a confounding variable:
- A study shows that wearing sunglasses and putting on sun cream are linked increases in sun cream sales are higher when sales of sunglasses increase. It could be that sun cream makes individuals wear sunglasses or that wearing sunglasses reminds people that they need to put on sun cream. However, there is a third "confounding" variable that affects

BOTH sales of sunglasses and sun cream - the weather. It could be that hot, sunny weather makes people both put on sunglasses and apply sun cream.

- Another example: In a case-control study on the association between cola drinking and type 2 diabetes => BMI is likely to be a confounding variable
- In general, a randomised controlled trial eliminates confounding by known and unknown factors.
- Stratified analysis eliminates the confounding of the stratified data.
- Multivariable logistic regression can control and minimise confounding by simultaneous adjustment for multiple factors.

Correlation and linear regression

Overview

- The terms correlation and regression are related but are not synonymous.
- Correlation is used to test for association between variables (e.g. whether salary and IQ are related).
- Once correlation between two variables has been shown regression can be used to predict values of other dependent variables from independent variables.
- Regression is not used unless two variables have firstly been shown to correlate.

Correlation

- The degree of correlation is summarised by the correlation coefficient (r). This indicates how closely the points lie to a line drawn through the plotted data. In parametric data this is called Pearson's correlation coefficient and can take any value between -1 to +1.
- The value of 'r' (coefficient of variation) ranges from -1 to +1
- For example
 - r = 1 strong positive correlation (e.g. systolic blood pressure always increases with age)
 - r = 0 no correlation (e.g. there is no correlation between systolic blood pressure and age)
 - r = 1 strong negative correlation (e.g. systolic blood pressure always decreases with age)
- Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they do not give information about how much the variable will change. They also do not provide information on cause and effect.
- Correlation is summarised when using parametric variables by Pearson's correlation coefficient (represented by a small r).
- In the situation of non parametric variables, Spearman's correlation coefficient is used.
 Spearman's correlation coefficient is usually represented by the Greek letter p (rho), or by rs.
- · In the case of dichotomous variables logistic regression is used.
- Linear (or simple linear) regression is used when looking for association between two
 continuous variables, and multiple regression is used when looking for association between
 more than two continuous variables.

Linear regression

- In contrast to the correlation coefficient, linear regression may be used to predict how much one variable changes when a second variable is changed.
- A regression equation may be formed, y = a + bx, where:

- y = the variable being calculated
- a = the intercept value, when x = 0
- b = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x
- x = the second variable

Correlation coefficient

- The correlation coefficient measures the strength (and direction, if linear) of the relationship between two variables.
- Correlation coefficient does not follow normal distribution.
- Calculation of correlation coefficient does not need to assume normal distribution.
- If there is perfect linear relationship with positive slope between the two variables, the correlation coefficient is 1.
- If there is a perfect linear relationship with negative slope between the two variables, the correlation coefficient is -1.
- A correlation coefficient of 0 means that there is no linear relationship between the variables.
- The correlation is not necessarily linear
- Correlation coefficient describes the linear relationship between two variables. If the relationship between them is not linear, it can be misleading and should not be used.
- The correlation coefficient does not depend on sample size. Increasing the sample size will not change the correlation coefficient as its value does not depends on sample size.
- The correlation coefficient can be a negative number.
- The correlation coefficient can range from -1 to +1.
- Correlation and regression are different.
 - ⇒ **Correlation** describes how closely two variables are associated.
 - ⇒ **Regression** allows you describe one variable with respect to the other in terms of an equation.

Screening test statistics

Sensitivity = true positives / (true positives + false negatives)

Specificity = true negatives / (true negatives + false positives)

The rule of thumb is that a high sensitivity helps to **rule out** disease (SnOut) and a high specificity helps to **rule in** (SpIn) disease (Mnemonic "spin and snout")

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Contingency tables

- also known as 2 * 2 tables, are used to illustrate and calculate test statistics such as sensitivity.
- TP = true positive; FP = false positive; TN = true negative; FN = false negative

	Disease present	Disease absent
Test positive	TP	FP
Test negative	FN	TN

The table below lists the main statistical terms used in relation to screening tests:

Measure	Formula	Plain English
Sensitivity	TP / (TP + FN)	Proportion of patients with the condition who have a positive test result
Specificity	TN / (TN + FP)	Proportion of patients without the condition who have a negative test result
Positive predictive value	TP/(TP+FP)	The chance that the patient has the condition if the diagnostic test is positive
Negative predictive value	TN / (TN + FN)	The chance that the patient does not have the condition if the diagnostic test is negative
Likelihood ratio for a positive test result	sensitivity / (1 - specificity)	How much the odds of the disease increase when a test is positive
Likelihood ratio for a negative test result	(1 - sensitivity) / specificity	How much the odds of the disease decrease when a test is negative

Sensitivity and specificity

- Essentially a knowledge of the sensitivity/specificity is based on the *disease* state itself, whereas predictive values are based on the test result.
- Sensitivity and specificity will not change with sample size. They will change only with:
 - ⇒ composition of the sample (especially if subjects in the sample have different risks of disease)
 - ⇒ performance of the test
 - ⇒ diagnostic threshold, and
 - ⇒ The "gold standard" to be compared with.
- The reliability of estimates of sensitivity, specificity, positive and negative predictive value will all increase with increasing sample size, which will reduce their confidence intervals.
- Increasing the cut-off of a positive test result will decrease the number of false positives and hence increase the specificity.

Positive and negative predictive values

- Positive and negative predictive values are prevalence dependent.
 - ⇒ The positive predictive value will increase and negative predictive value will decrease if the prevalence of the disease increases.

Likelihood ratios

- Likelihood ratios are not prevalence dependent.
- If the sensitivity increases, the likelihood ratio of a positive test will increase. If the specificity decreases, the likelihood ratio of a positive test will decrease.
- The likelihood ratio of negative test will increase if the specificity of the test is decreased.
- The lower the likelihood ratio of a negative test, the less likely is the presence of disease
- The likelihood ratio of a positive test helps to rule in disease and the likelihood ratio of a negative test helps to rule out disease.

Posterior probability

- Posterior probability = posterior odds / (1 + posterior odds)
 - ⇒ Posterior odds of having disease = prior odds × likelihood ratio.
 - ⇒ Prior odds of having disease = Prevalence(P) / (1 P)

Precision

quantifies a tests ability to produce the same measurements with repeated tests.

MRCPUK-part-1-September 2009 exam: What is the correct formula to calculate the negative predictive value of a screening test?

→ TN / (TN + FP)

Incidence and prevalence

Incidence is the number of new cases per population in a given time period.

Prevalence is the total number of cases per population at a particular point in time.

- These two terms are used to describe the frequency of a condition in a population.
- The **incidence** is the number of new cases per population in a given time period.
- For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.
- The **prevalence** is the total number of cases per population at a particular point in time.
- For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship

- prevalence = incidence * duration of condition
- in chronic diseases the prevalence is much greater than the incidence
- in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

Relative risk

Relative risk ratio (RRR) = EER / CER

- **Relative risk (RR)** is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER).
 - ⇒ EER = rate at which events occur in the experimental group
 - ⇒ CER = rate at which events occur in the control group
- For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	Total number of patients	Experienced significant pain relief
Paracetamol	100	60
Placebo	80	20

- Experimental event rate, EER = 60 / 100 = 0.6
 Control event rate, CER = 20 / 80 = 0.25
 Therefore the relative risk ratio = EER / CER = 0.6 / 0.25 = 2.4
- If the risk ratio is > 1 then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls. It is therefore appropriate to calculate the relative risk increase if necessary (see below).
- If the risk ratio is < 1 then the rate of an event is decreased compared to controls. The relative risk reduction should therefore be calculated (see below).
- . The relative risk is always positive
- Relative risk reduction (RRR) or relative risk increase (RRI) is calculated by dividing the absolute risk change by the control event rate
 Using the above data, RRI = (EER - CER) / CER = (0.6 - 0.25) / 0.25 = 1.4 = 140%
- Relative risk reduction = 1 relative risk

Remember that risk and odds are different. If 20 patients die out of every 100 who have a myocardial infarction, then the risk of dying is 20 / 100 = 0.2 whereas the odds are 20 / 80 = 0.25.

Numbers needed to treat and absolute risk reduction

NNT= 1/absolute risk reduction

Absolute risk reduction = (Control event rate) - (Experimental event rate)

- Numbers needed to treat (NNT) is a measure that indicates how many patients would require an intervention to reduce the expected number of outcomes by one.
- Example: if a study for stroke reveals that 20 patients need to be treated to prevent one event.
- That means, if you treat a 1000 patients then you will expect to have 50 fewer strokes

- It is calculated by 1/(Absolute risk reduction)
 Experimental event rate (EER) = (Number who had particular outcome with the intervention) / (Total number who had the intervention)
- **Control event rate (CER)** = (Number who had particular outcome with the control/ (Total number who had the control)
- Absolute risk reduction = CER-EER or EER-CER
- ARR = risk in control group risk in treated group.
 - ⇒ For example: If a drug reduces the incidence of heart attacks from 12% to 8% then:
 - The control event rate (CER) is 12%
 - The experimental event rate (EER) is 8%
 - The relative risk reduction (RRR) is 33% ([EER-CER/CER] x 100)
 - The absolute risk reduction (ARR) is 4% (CER-EER)
 - The number needed to treat (NNT) is 25 ([1/ARR] x 100)

Number needed to harm

For many studies now, papers quote the number needed to harm. This uses the same
principle to establish the difference in absolute risk of an adverse event occurring between
two treatment strategies, calculating a number needed to harm by dividing 100 by the
absolute risk.

Hazard ratio

- The hazard ratio (HR) is similar to relative risk but is used when risk is not constant to time. It is typically used when analysing survival over time
- Example: A study is performed comparing two chemotherapy regimes for patients with small cell lung cancer. The end point of the study is survival time. Which one of the following types statistical measures is it most appropriate to compare survival time with? → Hazard ratio

Odds and odds ratio

Odds - remember a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome

NOT a ratio of the number of people who incur a particular outcome to the total number of people

 Odds are a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome. The odds ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

Odds vs. probability

In contrast, probability is the fraction of times you'd expect to see an event in many trials. When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:

- the probability of rolling a six is 1/6 or 0.166666
- the odds of rolling a six is 1/5 or 0.2
- Odds ratios are the usual reported measure in case-control studies. It approximates to relative risk if the outcome of interest is rare.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

	4	
h	4	h
v	-	v

	Total number of patients	Achieved = 50% pain relief
Paracetamol	60	40
Placebo	90	30

The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2

The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5

Therefore the odds ratio = 2 / 0.5 = 4

Pre- and post- test odds and probability

Pre and post-test odds

- Pre-test odds
 - ⇒ The odds that the patient has the target disorder before the test is carried out
 - ⇒ Pre-test odds = (pre-test probability/[1 pre-test probability]).
- Post-test odds
 - ⇒ The odds that the patient has the target disorder after the test is carried out
 - ⇒ Post-test odds = (pre-test odds x likelihood ratio).
 - ⇒ the likelihood ratio for a positive test result = sensitivity / (1 specificity).

Pre and post-test probability

- Pre-test probability
 - ⇒ the proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence).
 - ⇒ For example, the prevalence of rheumatoid arthritis in the UK is 1%.
- Post-test probability
 - ⇒ The proportion of patients with that particular test result who have the target disorder
 - ⇒ Post-test probability = (post-test odds/[1 + post-test odds]).

Screening: Wilson and Junger criteria

- 1. The condition should be an important public health problem
- 2. There should be an acceptable treatment for patients with recognised disease
- 3. Facilities for diagnosis and treatment should be available
- 4. There should be a recognised latent or early symptomatic stage
- **5.** The natural history of the condition, including its development from latent to declared disease should be adequately understood
- 6. There should be a suitable test or examination
- 7. The test or examination should be acceptable to the population
- 8. There should be agreed policy on whom to treat
- **9.** The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole
- 10. Case-finding should be a continuous process and not a 'once and for all' project

R-values

- A positive R-value means that as one variable increases, so does the other
- A negative R-value means that as one variable decreases, the other increases ie the correlation is inversed (A negative R-value indicates an inverse association)
- association or lack of association is indicated by how close the value of R is to zero
- statistical significance is denoted by its **p**-value
- P-values < 0.05 are considered to be significant

Scales of measurement

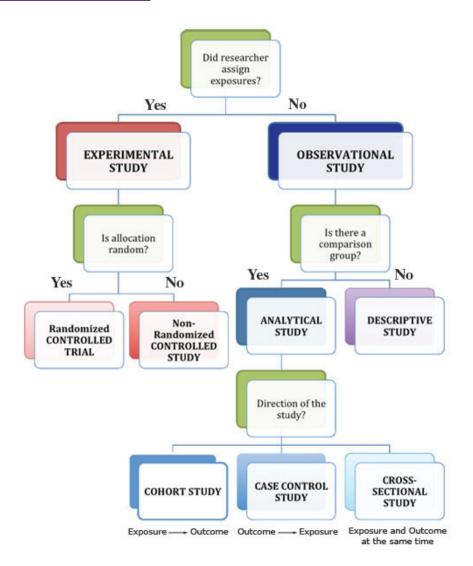
Data always come in one of the four scales of measurement:

Nominal	Data are divided into qualitative groups, such as hot/cold, with no implication of order.
Ordinal	Data are placed in an order (hot/hotter/hottest), although the absolute levels are
	unknown and no conclusion can be made about the size of the interval.
Interval	dividing a continuous measurement into groups (eg age groups). Data are placed in an order; and the exact value of the measurement is given, usually in measured quantities representing the difference between two measurements (81-90/91-100/101-110 °C). That is, differences between arbitrary pairs of measurements can be meaningfully compared. Ratios between numbers of the scale are not meaningful, so operations such as multiplication and division cannot be carried out directly. But ratios of differences can be expressed; for example, one difference can be twice Another If the measurement scale does not have an absolute zero (ie no numbers exist below the zero) this is called interval data.
Ratio	Here, there is a value of 0 kelvin, and it isn't possible to get below this (ie absolute zero), therefore, the ratio between the values is meaningful, eg 271-280/281-290/291-300 kelvin.

Select Study Design to Match the Research Goals

Objective	Study design
Describe of disease or spectrum	Case series or report Cross sectional study
Determine operating characteristics of a new diagnostic test	Cross sectional study
Describe prognosis	Cohort study
Determine cause-effect	Cohort study Case control study
Compare new interventions	Randomised clinical trial
summarize literature	Meta-analysis

Select Study Design



The following table highlights the main features of the main types of study:

Study type	Key features
Randomised controlled trial	Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo) Practical or ethical problems may limit use
Cohort study	Observational and prospective. Two (or more)are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome. The usual outcome measure is the relative risk. Examples include Framingham Heart Study
Case-control study	Observational and retrospective. Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition. The usual outcome measure is the odds ratio. Inexpensive, produce quick results Useful for studying rare conditions Prone to confounding
Cross-sectional survey	Provide a 'snapshot', sometimes called prevalence studies Provide weak evidence of cause and effect

Systematic review (meta-analysis)

Funnel plots - show publication bias in meta-analyses

- a study of studies.
- statistical (quantitative) combination of results from two or more studies addressing the same research question.
- Metanalysis= systematic reviews + Quantitative measures.
- Usually used to treatment studies.
- A 'meta-analysis' would look at combining all previous data,. This is likely to be the
 quickest option to complete, and also produces the highest level of evidence.
- rapid and efficient
- Publication bias might be present (positive results are published more often than the negative ones).
- Publication bias can be examined by funnel plots if a sufficient number of studies is found.
- Non-randomised or other studies may or may not be included.
- However, randomised controlled trials usually have lower risk of bias and hence give us more confidence about validity of results and are preferred primary sources for systematic review.
- Critical appraisal is an important part of systematic review and it has to be objectively performed using well-defined criteria or appraisal tools.

- Meta-analysis, that is, combining results numerically in a statistically appropriate way, though desirable, is not always feasible, depending on the availability of usable data and heterogeneity. (Meta-analysis is not always performed)
- The search strategy in systematic review should be comprehensive involving electronic databases and other sources and using well-defined search terms.
- Case-control studies are not usually included in the search of literature in systematic review
- · The research question is always focused
- there are at least two authors to independently appraise the search results and primary studies.
- · It is not mandatory to exclude studies with missing data.
- The effect size should not affect the weight of each study, although it will affect the final result.
- Trial quality is usually not incorporated into meta-analysis nowadays since the weightings can be subjective and arbitrary.
- · The weight of each study should depend on the sample size
- Funnel plots
 - ⇒ show publication bias in meta-analyses
- Forest plot
 - ⇒ The most appropriate way of graphically depicting the results of metaanalysis.

Fixed vs random effect model for meta-analysis

The fixed effect model	The random effects model
the most commonly used model for meta-analysis. Provides the best estimate of the treatment effect	
attempts to provide one single best estimate of treatment effect.	attempts to find an average treatment effect.
assumes there is no heterogeneity between the trials.	assumes heterogeneity
assumes a single treatment effect	allows multiple treatment effects.

Randomised controlled trial (RCT)

Overview

• The purpose of randomisation is to prevent systematic differences (bias) between treatment groups.

Aim: to determine the possible effect of a specific intervention on a given population

Advantages

- · Minimizes bias
- Can demonstrate causality

Disadvantages

· Cannot be used to evaluate rare diseases

- ⇒ For rare diseases and exposures, case control studies are the best option. Although cohort studies are good for rare exposures, they are not good for rare diseases.
- Cannot be used when treatments have well-known adverse side effects
- Expensive and time-consuming

Uses

- the 'gold standard' for evaluating a new intervention
- May be used to test an efficacy of a drug

Study method

- Randomization: Study participants are randomly allocated to either the
 treatment/intervention group or the control group to ensure that both groups have
 approximately the same baseline characteristics.
- **Blinding:** the practice of not informing an individual or group about which study participants are part of the control group and which are part of the treatment group (used to reduce bias)

Classic errors in randomisation

- ⇔ Consecutive sampling, which may well not be representative if the study time is short.
- ⇒ Convenience sampling: strong potential for bias, with volunteers generally healthier than others.
- ⇒ Judgmental sample: including those that you want only. The potential for systematic error is enormous.

Methods of analysis for randomized controlled trials

Intention to treat analysis (ITT)

- Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment. Include the patients who drop out in the final data set
- ⇒ Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups.
- ➡ ITT helps to reduce bias by sticking to the original allocation of treatment and analysing the patient in that treatment group even if they do not receive the treatment
- ⇒ ITT is considered to be the analysis which is least subject to bias. Considered the most robust

Per protocol analysis

A per protocol analysis may exclude patients who suffered an event but then did not follow the protocol accurately, for example, a patient treated with the diabetes agent who was admitted to hospital, but missed one to two doses of medication.

Case-control study

A case-control study generally examines a small population group over a short period of time (less cost-intensive) and evaluates the association between multiple exposures and one outcome.

A cohort study generally examines a large population over a long period of time (more cost-intensive) and determines how one exposure is associated with multiple

Aim

• to study if an exposure (i.e., a risk factor) is associated with an outcome (i.e., disease)

Study method

- Researchers begin by selecting patients with the disease (cases) and individuals without the disease (controls).
- Controls are selected from the same source population and ideally have similar characteristics (e.g., gender, age) to the cases to reduce potential confounding.
- The odds ratio is then determined between these groups.

Advantages

- Can be used to study rare diseases
- Can be used to study diseases with long latency periods
- · A wide range of risk factors can be investigated
- · There is no loss to follow up
- They are relatively cheap and guick to perform.

Disadvantages

- Recall and/or survivorship bias occurs in retrospective studies (have the greatest problems with recall bias)
- Cannot be used to determine prevalence or incidence

Example

A group of patients with histologically confirmed cervical cancer (cases) is compared to
otherwise similar patients without histologically confirmed cervical cancer (controls) for the
presence of human papillomavirus (exposure).

Cohort study

In cohort studies, the study sample is selected based on exposure to a risk factor.

In case-control studies, the study sample is selected according to having a disease or not, and then it is determined which participants were exposed to a risk factor.

Aim

To study the incidence rate and whether a given exposure is associated with the outcome
of interest

Study method

- The researchers gather a group of study participants who have common characteristics.
- Participants are then classified into two groups: exposed and unexposed.
- The incidence of the outcome of interest is compared between the two groups.

Advantages

- · Less susceptible to recall bias than case-control studies.
- Helps determine whether a given exposure plays a role in the development of a disease
- Allows for the calculation of relative **risk**
- Helps determine incidence
- Can be used for rare exposures

Disadvantages

- When the outcome of interest is rare a very large sample size is needed (Insufficient for rare disease)
- Prospective cohort studies are high-cost and time-consuming
- In retrospective cohort studies, some data on predictors and confounders may be missing because the data was collected in the past.
- Only assesses the exposures determined at the beginning of the study

Types

	Types of cohort studies				
	Prospective cohort study	Retrospective cohort study			
Description	Study begins before the groups	Study begins after the exposure and			
	develop an outcome of interest	outcome of interest have already occurred			
Exposure	Study participants are categorized	Study participants are categorized into a			
	into an exposed group and an	group that was previously exposed to a given			
	unexposed group.	risk factor (exposed; e.g., smoking) and a			
		group that was not (unexposed).			
Outcome	The participants	Data previously collected about the			
	are followed prospectively for	participants is compared to see whether			
	a period of time to see whether	there was a difference in the rate at which			
	there is a difference in the rate at	the exposed and unexposed groups			
	which the exposed and unexposed	developed the outcome of interest (e.g., lung			
	groups develop the outcome of	cancer) over a period of time.			
	interest.				
Example	Individuals with a smoking history of ≥ 1	Individuals with a smoking history of ≥ 1 pack			
	pack of cigarettes a day (exposed	of cigarettes a day (exposed group) 5 years			
	group) are compared to individuals who	ago are compared to individuals who were			
	are non-smokers to see if there is a	non-smokers 5 years ago to see if there is a			
	difference in the proportion of patients in	difference in the proportion of patients in			
	each group that develop lung cancer	each group that eventually develop			
	(e.g., the outcome) within a specific				
	follow-up period.				

Observational study

- Disadvantages
 - ⇒ From association in an observational study, we cannot infer cause and effect

Biological assays

 Biological assays are designed to measure the relative <u>potency</u> of different preparations.

Sequential trial

- a trial in which the data are analysed after each participant's results become available and
 the trial continues until a clear benefit is seen in one of the comparison groups, could also
 be used to assess efficacy, but there would have to be a large expected difference from
 placebo.
- 'Sequential' trial would be comparing one therapy to another sequentially (usually with wash out periods in between).

Crossover trial

- ⊃ The principle of a crossover design is that a patient has one drug or treatment, then a washout period, and then another drug, and the effect is compared between the two in a single individual.
- ⇒ For this reason it is a good study design for treatment of chronic conditions (eg: comparing analgesics in arthritis) but not appropriate for acute conditions.
- In a crossover trial, the patient (who usually has a chronic stable disease) receives
 one drug (or placebo) and then the other drug after a washout period
- · Each patient will usually receive all drugs within the study
- In this way, confounding can be greatly reduced
- If a drug had long-lasting effects it may not be easy to see which of the trial drugs was having an effect
- A self-limiting illness is difficult to study in this way
- Because each person is acting as their own control, it is usually possible to use smaller numbers to get the same power.
- If any treatment in a cross-over trial is a disease-modifier (in the most extreme case, kills or cures the patient), then the interpretation of results in any subsequent period becomes impossible. This is because disease modification implies that one course of the drug will permanently change the future timecourse of that patient's disease in some way, making a cross-over study un-interpretable. In this case a parallel trial is the only appropriate option.

Sampling

- Sampling error arises when only a portion of the population is studied
- Random sampling implies that the sample has been selected from a sampling frame in such a way that every individual has the same chance of being selected
- The standard error of the mean is the standard deviation divided by the square root of the sample size, hence it must always be smaller than the standard deviation
- Inference is the process of drawing conclusions about the population using the sample information
- a sample statistic is a point estimate of a population parameter

Bias (Systematic error)

Definition

 An error in the study design or the way in which the study is conducted that causes systematic deviation of findings from the true value

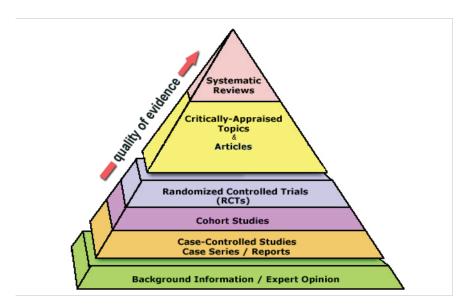
Types

- **Selection bias** occurs when the study population is different from the population to whom the results will be applied and there is therefore said to be
- Allocation bias occurs when patients are not randomly assigned to a particular treatment.
- Assessment bias occurs when the observer knows which treatment the subject is taking.
- Observer bias is when one observer consistently under or over reports a particular variable
- **Recall bias** applies to case-control studies when a patient is more likely to remember a particular detail of exposure if they go on to develop the disease.

Study design: evidence and recommendations

Levels of evidence

- la evidence from meta-analysis of randomised controlled trials
- Ib evidence from at least one randomised controlled trial
- Ila evidence from at least one well designed controlled trial which is not randomised
- IIb evidence from at least one well designed experimental trial
- III evidence from case, correlation and comparative studies
- IV evidence from a panel of experts



Grading of recommendation

- Grade A based on evidence from at least one randomised controlled trial (i.e. la or lb)
- Grade B based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
- Grade C based on evidence from a panel of experts (i.e. IV)

Study design: new drugs

Superiority trial → a large sample size is required to demonstrate a significant difference

When a new drug is launched there are a number of options available in terms of study design. One option is a placebo-controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments.

Compare a new drug to an existing treatment

- The statistician need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:
- Superiority
 - ⇒ one problem is the large sample size needed to show a significant benefit over an existing treatment
- Equivalence
 - ⇒ an equivalence margin is defined (-delta to +delta) on a specified outcome. If the
 confidence interval of the difference between the two drugs lies within the
 equivalence margin then the drugs may be assumed to have a similar effect

Non-inferiority

- ⇒ similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta).
- ⇒ Small sample sizes are needed for these trials.
- ⇒ Once a drug has been shown to be non-inferior large studies may be performed to show superiority
- It should be remembered that drug companies may not necessarily want to show superiority
 over an existing product. If it can be demonstrated that their product is equivalent or even
 non-inferior then they may compete on price or convenience.

Phases of new drug development

phase	goal	notes
Animal trial	Safety for testing the drug in humans	
Phase I	 Initial safety most frequent side effects How the drug is metabolized and excreted. 	 conducted in healthy volunteers. The number of subjects ranges from 20 to 80.
Phase II	Effectiveness (RCTs)	The number of subjects ranges from a few dozen to about 300.
Phase III	Comparative efficacy (Effectiveness compared to commonly used treatment)	 The number of subjects ranges from several hundred to about 3,000 The best study for phase 3 is a randomised control study.
Phase IV (post marketing)	Side effects	Enrolls a large number of patients, typically several thousands.

Graphical representation of data

Charts and diagrams

Quantitative data	Qualitative data
Histogram	Bar diagram
Scatter diagram	Pie diagram

The interpretation of novel findings in a published clinical research study

- The trustworthiness of a study should depend solely on its scientific validity, that is, whether
 it is free of bias.
- The conclusion should be treated with skepticism even if it is extensively peerreviewed



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